Brain

A Journal of Neurology

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MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON
NEW YORK: THE MACMILLAN COMPANY

Vol. 63. Part 4. 1940 **Price 6s. net. Subscription, 24s. net.**

Entered as Second Class Matter, April 24, 1929, at the Post Office at Boston, Mass., under the Act of March 3, 1897 (Sec. 397, P.L. and R.). Printed in Great Britain.

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DECEMBER, 1940

BRAIN

VOL. 63, PART 4.

VASOMOTOR REFLEXES IN THE CONTROL OF BODY TEMPERATURE IN MAN.

BY J. J. R. DUTHIE AND R. M. I. MACKAY.

From the Wilkie Surgical Research Laboratory.

PART I.

REFLEX VASODILATATION IN RESPONSE TO A RISE IN SKIN TEMPERATURE IN MAN.

INTRODUCTION.

IN mammals the maintenance of a relatively constant internal temperature depends on the existence of a delicate heat-regulating mechanism whereby the animal can maintain a high degree of activity under widely varying environmental conditions. The relatively small fluctuations in body temperature which take place normally imply a control which can adjust the balance between heat production and heat loss with great rapidity. Variations in heat production would be a clumsy method of maintaining a constant body temperature, so regulation must depend largely on variations in heat elimination. Since in temperate climates about 70 per cent. of heat loss takes place by radiation and conduction from the skin, it is evident that temperature control must depend largely on the regulation of cutaneous circulation.

Local application of heat causes vasodilatation and cold causes vasoconstriction of the skin vessels (Lewis, 1927). If the stimulus is sufficiently intense and is applied over a wide enough area of skin, corresponding vascular changes occur in distant areas. Brown-Séquard and Tholozan (1858) showed that immersion of one hand in ice water produced a cooling in the other hand. François-Franck (1876) confirmed this observation by demonstrating plethysmographically that touching one hand with a block of

ice for one second caused vasoconstriction in the other. Using a calorimeter, Stewart (1911) showed that immersion of one hand in cold or hot water caused a marked decrease or increase respectively in the blood-flow in the opposite hand. Lewis and Pickering (1931) produced evidence to show that these distant vascular changes were dependent on the sympathetic fibres supplying the blood-vessels in the skin. By the method of Landis and Gibbon (1932) it can be shown that immersion of the forearms in warm water causes vasodilatation in the lower extremities. That general vasoconstriction following the local application of cold depends on afferent sensory impulses arising in the cooled skin has been confirmed by many workers. François-Franck (1876) found that repeatedly touching one hand with ice led to a gradual lengthening of the interval between the application of the stimulus and the appearance of vasoconstriction in the other hand, until finally no response was obtainable. He concluded therefore that this was reflex in origin. This was confirmed by Fredericq (1882) who showed that immersion in cold water of the hind leg of a rabbit caused vasoconstriction in the opposite foot, only if both sciatic nerves were intact. Grant and Bland (1933) found that denervation of a rabbit's ear banished the vasoconstrictor response to cooling of the opposite ear, which they had demonstrated in normal animals. Rein (1931) produced evidence to show that exposure of an animal to cold caused a marked increase in the blood-flow through the internal organs. He also noted that the skin around the dog's nose was highly sensitive to changes in temperature. Cool air blown on this area caused an increase in blood-flow in the carotid artery; the response occurred in 0·5 second and ceased immediately cooling was stopped. He concluded that these vascular responses were the result of reflex activity. Pickering (1932) found that application of cold to an arm, the circulation in which had been arrested, caused conspicuous vasoconstriction in the opposite hand.

From these observations it can be accepted that the application of cold to the skin causes widespread reflex vasoconstriction, thus diminishing heat loss, and preventing a fall in body temperature. As has already been stated, heat applied locally will cause general vasodilatation and an increase in heat elimination. Many workers believed that this reaction was also dependent on reflex activity. Rein (1931) concluded from his experiments on animals that temperature regulation was controlled by vasomotor reflexes, on the ground that the responses obtained on the application of heat and cold occurred too rapidly to be dependent on the changes in blood temperature. Winkler (1902) working with rabbits showed that after section of the thoracic spinal cord, immersion of the insensitive hind quarters in

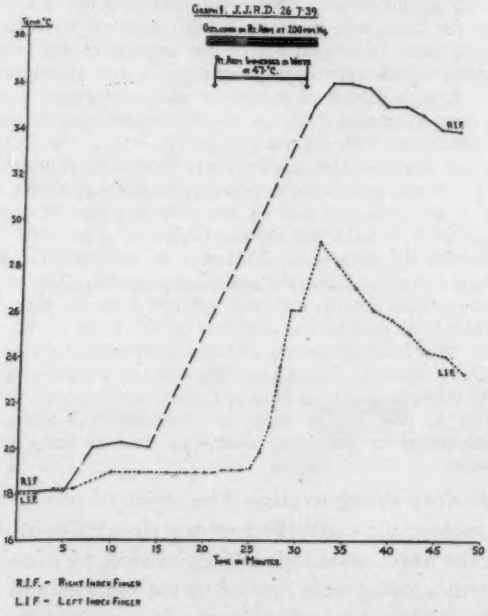
warm water was followed by flushing of the ears only after a long delay. He concluded that vasodilatation of the ears took place only after the thermo-sensitive forequarters had become warm, and that the results were due to reflex stimulation of the thermo-sensitive nerve-endings in their skin. Ruhmann (1927) observed that when heat was applied to the skin of the abdomen, hyperæmia of the gut was produced. He concluded that it was a reflex effect caused by stimulation of thermo-sensitive endings in the skin. Stewart (1911) believed that the increase in blood-flow which occurred in one hand when the other was immersed in hot water was due to a vasomotor reflex, because of the promptness of the response.

On the other hand, there is a great deal of evidence in favour of the hypothesis that the widespread vasodilatation which occurs when heat is applied to one or more limbs, depends not on reflex activity, but on a rise in blood temperature which acts on a thermo-sensitive centre in the hypothalamus. It would appear that a rise in the temperature of the blood, acting through this centre, causes vasodilatation of the skin vessels, with a corresponding increase in heat elimination. Kahn (1904) showed that warming the blood in the carotid artery of dogs, cats and rabbits, caused dilatation of the skin vessels of the pads, and sweating. Moorhouse (1911) in carefully controlled experiments confirmed these observations. Barbour (1912), using dogs, heated the brain in the region of the lateral ventricle and produced a fall in body temperature. Cooling of this region produced a rise in body temperature. He concluded that these changes were due to peripheral vasodilatation and vasoconstriction respectively. Hashimoto (1915), using a similar technique in cats and rabbits, succeeded in cooling one side of the brain and heating the other. He sometimes obtained a simultaneous vasoconstriction in one ear and vasodilatation in the other. Prince and Hahn (1918) confirmed Barbour's results in the cat. Hill (1921) noted that a subject in a hot room (38° C.) began to sweat ; when the hands were put in cold running water sweating ceased, but if the circulation to the arms was arrested cooling of the hands no longer inhibited sweating, evidence that the regulation of the body temperature by sweating depends on a rise in blood temperature. Sherrington (1924), using dogs after transection of the spinal cord, produced shivering in the forequarters of these animals cranial to the spinal lesion by immersing the insensitive hindquarters in cold water, although the skin of the fore-quarters remained warm to the touch. No shivering occurred in the paraplegic portion. He suggested that shivering was caused by direct cooling of a central thermotaxic mechanism. Gibbon and Landis (1932) produced a rise in skin temperature in the lower extremities of human subjects in fifteen minutes by

immersing the forearms in warm water (43° to 45° C.). Similarly, heating of one forearm and one leg led to a rise in temperature in the other extremities. Heating one arm, the circulation of which had been arrested, produced no rise in skin temperature in the opposite hand. They also observed that in a patient with transverse myelitis, heating of the legs was followed by a rise in the temperature of the hands. From these experiments they concluded that the rise in temperature of the unheated limbs was due to warm blood heating a thermo-regulating centre, and not to reflex activity. Pickering (1932) concluded that application of heat to the skin does not produce reflex vasodilatation, and that the vasodilatation that does occur is due solely to the action of warmed blood on a central mechanism. The rise in blood temperature necessary to produce this effect was found to be about 0·01° to 0·04° C. In his experiments, heating an arm with its circulation occluded did not increase heat elimination from the opposite hand. Korth and Proger (1934) in the course of an investigation of the temperature of venous blood in the forearm, heated an occluded arm and found no rise in venous temperature in the opposite forearm. Uprus, Gaylor and Carmichael (1935, 1936) and Uprus, Gaylor, Williams and Carmichael (1935) during the investigation of the vasomotor responses in normal subjects and in patients suffering from various cerebral lesions found that a rise or fall in rectal temperature always preceded vasodilatation or vasoconstriction of the cutaneous vessels in response to heating or cooling the legs. They also observed that in two patients with transverse lesions of the cord at the level of the 12th thoracic segment warming of the legs caused vasodilatation of the hands.

Work by Keller (1933), Keller and Hare (1932), Bazett, Alpers and Erb (1933), and Ransom and Ingram (1935), indicates that the centre for heat regulation is situated in the hypothalamus. Hasama (1929) found that a fall in body temperature followed heating of the hypothalamus and preoptic region in the cat, and observed profuse sweating on the foot pads during this procedure. Magoun, Harrison, Brobeck and Ransom (1938) heated the region of the hypothalamus in cats and produced marked acceleration of the respiratory rate, panting, and in some instances the appearance of sweat on the foot pads. They interpreted their results as showing the existence of structures which are sensitive to changes in blood temperature whose function it is to increase heat elimination in the normal animal when a rise in blood temperature occurs. Rogers (1920) showed that removal of the cerebral hemispheres and thalami in pigeons led to a loss of temperature regulation. Bazett and Penfield (1922) found in cats that removal of all the brain above the level of the pons banished temper-

ature control. The role of the hypothalamus in temperature regulation is fully reviewed by Fulton (1938). He states that the hypothalamic nuclei are responsive both to reflex activation through the thermal receptors in the skin and to the temperature of the blood circulating through the region. Ample experimental evidence has been produced to show that the hypothalamic nuclei are sensitive to changes in blood temperature, but definite proof that they can be stimulated by afferent impulses arising as a result of temperature changes in the skin is lacking. In fact much of the recent work is against such a hypothesis.



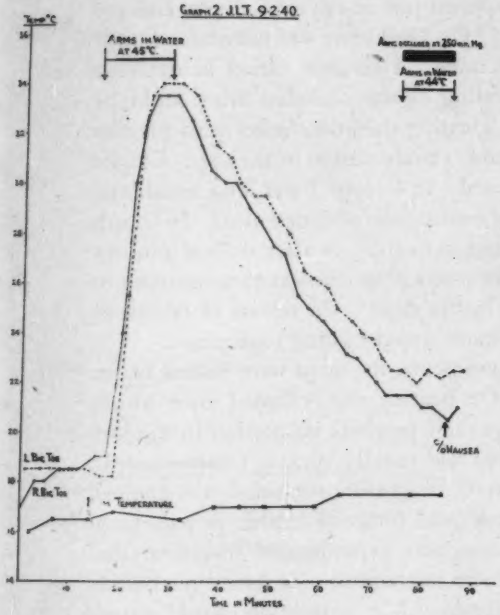
During an investigation of the local effects of heat applied to the skin, the following experiment was performed by one of us. The right arm was immersed in water at 14° C. for eight minutes. The circulation to the arm was then arrested by a sphygmomanometer cuff at 200 mm. Hg. The arm was immersed in water at 45° C. A copper-constantan thermocouple was applied to the left index finger and the skin temperature changes recorded during the heating of the occluded arm. It will be seen from Graph 1 that after five minutes heating a sudden and rapid rise in temperature occurred in the left index finger. Following withdrawal of the arm from the hot

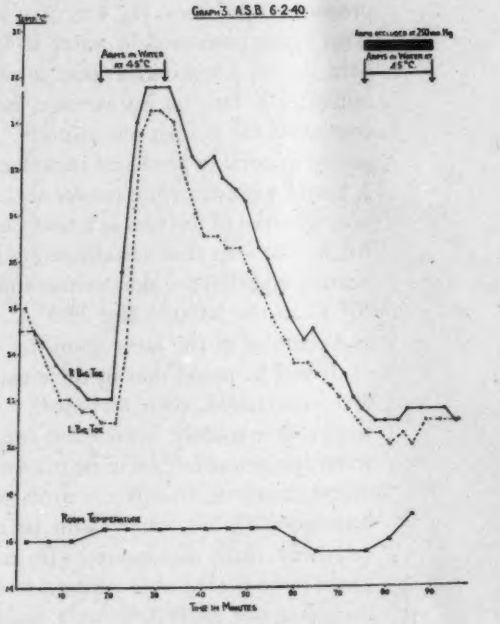
water and release of the circulation, the left index finger cooled fairly rapidly. The fact that the circulation in the heated limb was arrested excluded any rise in blood temperature as the cause of the vasodilatation noted in the skin of the left index finger. This suggested that in certain circumstances application of heat to the skin could give rise to reflex vasodilatation. It was decided to investigate this more fully, and the object of this paper is to present the results obtained.

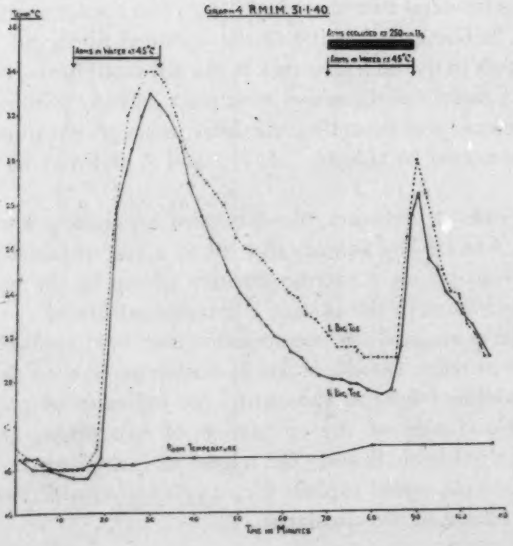
Method.

Variations in the cutaneous circulation in the fingers and toes were recorded by changes in the skin temperature as measured by copper-constantan thermocouples connected to a string galvanometer. The instrument used was that supplied by the Cambridge Instrument Company, the scale being calibrated to record the temperature in degrees centigrade. The accuracy of the instrument was checked against a sensitive thermometer before experiments were begun and at intervals throughout the investigation. A high degree of sensitivity was unnecessary as the significant variations in skin temperature were always of considerable magnitude. The galvanometer recorded temperature with accuracy to within 0·5° C. In order to allow the use of more than one thermocouple, a switch was incorporated which enabled three couples to be used. The couples were applied on the palmar aspect of the terminal phalanges of one or more fingers, and on the plantar aspect of one or more toes. Adhesive tape was used to hold the thermocouples in place, care being taken to avoid interference with the peripheral circulation by constriction. This method of application was found to give uniformly satisfactory results. The experiments were carried out at room temperature with the subjects wearing their usual clothing except for the removal of jackets and exposure of the arms to the elbows and the legs to the knees. Thermostatic control of room temperature was not possible, but it remained relatively constant throughout the majority of the experiments. Heat was applied to the subjects by the method of Landis and Gibbon (1932)—immersion of either the arms or the legs in water at about 45° C. When occlusion was applied, sphygmomanometer cuffs were used, the pressure being rapidly raised to 200 mm.Hg or over.

Results in healthy young adults.—The object of our first three experiments was to discover the exact effect on the circulation in the skin of the toes of heating the arms, unoccluded and occluded, by immersion in water at 45° C. Thermocouples were applied to the big toes and readings were taken every two minutes until the skin temperature had become relatively stable. Room temperature varied between 16° C. and 17° C. When the skin temperature had been stable for about ten minutes, both forearms were immersed in water at 45° C. until relatively full vasodilatation had occurred in the toes, as shown by skin temperatures between 32° to 36° C. This took place in ten to fifteen minutes. These results are comparable with those obtained by Landis and Gibbon (1932). The arms were then removed from the hot water and readings continued until the temperature of the skin of the toes had fallen to within a few degrees of the initial temperature. This usually occurred in forty-five to fifty minutes. An occlusion


Graph 2 JLT 9-2-40
Temp °C
Arms in Water at 45°C
Arms occluded at 250 mm. Hg
Arms in Water at 44°C
L. Buc. Tem
R. Buc. Tem
Temperature
Time in Minutes


Graph 3 ASB 6-2-40.
Temp °C
Arms in Water at 45°C
Arms occluded at 250 mm Hg
Arms in Water at 45°C
R. Buc. Tem
L. Buc. Tem
Room Temperature
Time in Minutes


Graph 4 RMIM. 31-1-40
Temp °C
Arms in Water at 45°C
Arms occluded at 250 mm Hg
Arms in Water at 45°C
L. Buc. Tem
R. Buc. Tem
Room Temperature
Time in Minutes

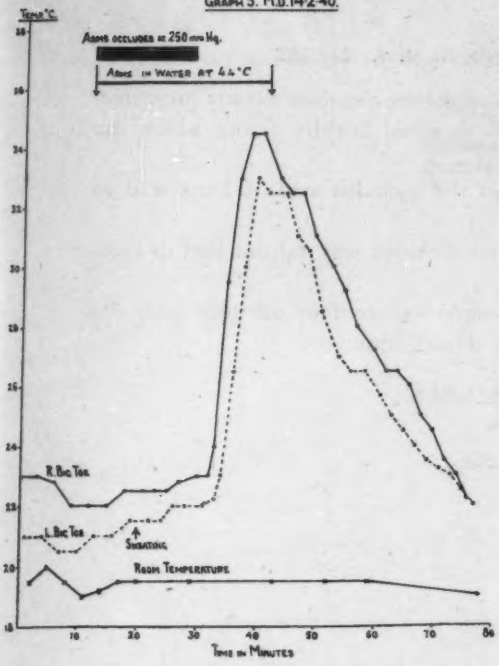
pressure of 250 mm. Hg was then applied just above each elbow, and the arms again immersed in water at 45° C. Occlusion was maintained until pain in the forearms became intolerable. Tolerance varied in different individuals, but, on an average, heating of the occluded arms could be continued for at least ten minutes. Heating the unoccluded arms for this period invariably produced considerable vasodilatation in the toes. Graphs 2, 3, and 4 illustrate the results obtained. In Graphs 2 and 3 no vasodilatation occurred in the toes as a result of heating the occluded arms. In Graph 4 it will be seen that vasodilatation began in the toes after sixteen minutes heating and that the skin temperature rose within the next three minutes to 30° C. in the left toe and 28·5° C. in the right. On release of occlusion and removal of the arms from the water, rapid cooling took place.

It will be noted that in these experiments, the arms were heated twice, first unoccluded, then occluded. On heating the occluded arms which were still markedly hyperæmic from their previous immersion in the hot water, pain was felt early in the arms and rapidly became severe. It was found, however, that if the arms were cold before occlusion was applied immersion in hot water could be tolerated for considerable periods with relatively little discomfort. In subsequent experiments, therefore, the limbs to be heated were exposed to room temperature for some time before occlusion was applied, or were rapidly cooled by immersion in cold water. The circulation was then arrested by pressures of 200 mm. Hg or over and the cold limbs immersed in water at 45° C. The results obtained fall into two groups. In Group 1, heating of the occluded limbs did not give rise to vasodilatation in the fingers or toes of the unheated limbs, but on release of occlusion a rapid vasodilatation took place starting within two to four minutes of release and becoming maximal in six to ten minutes. These results are illustrated by Graphs 5, 6, 7, 8 and 9, and may be explained in two ways.

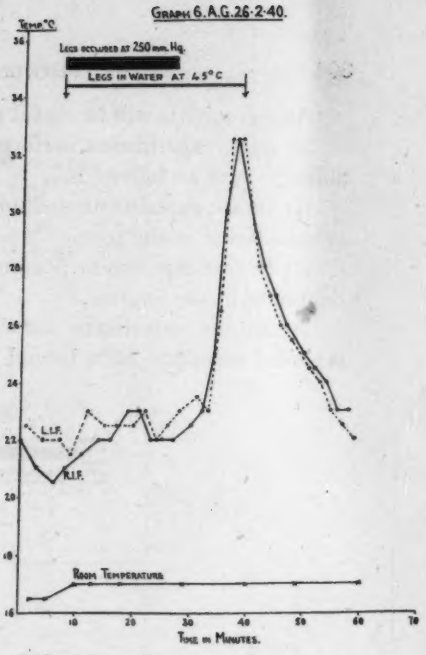
(1) On release of occlusion, blood entered an already warm and vasodilated limb, was rapidly heated, and led to a rise in blood temperature, which, by its action on a thermo-sensitive centre in the hypothalamus, caused vasodilatation in the skin of the unheated limbs.

(2) If it be postulated for the moment that heat applied to the skin does give rise to reflex vasodilatation in distant parts, then the reflex may have been inhibited by the vasoconstrictor influence of painful stimuli arising from occlusion of the circulation of two limbs, and from the heating of the ischæmic limbs. On release of occlusion pain disappeared immediately. This would explain the rapidity with which vasodilatation followed the release of the circulation.

GRAPH 5. M.D. 14-2-40.

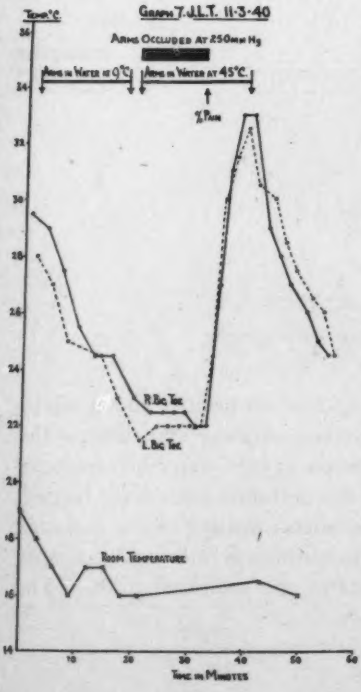


GRAPH 6. A.G. 26-2-40.

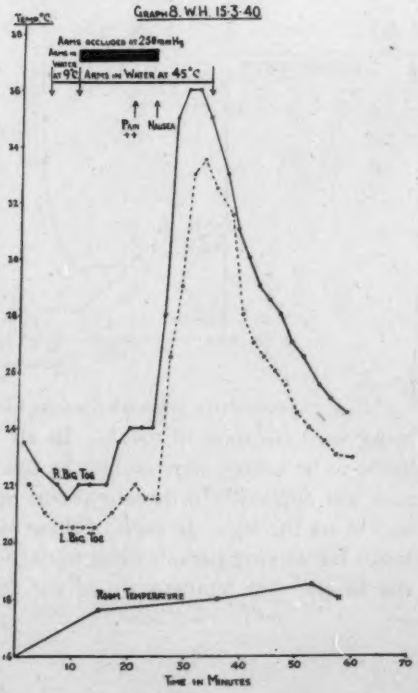


L.I.F. — LEFT INDEX FINGER
R.I.F — RIGHT INDEX FINGER

GRAPH 7. J.L.T. 11-3-40



GRAPH 8. W.H. 15-3-40



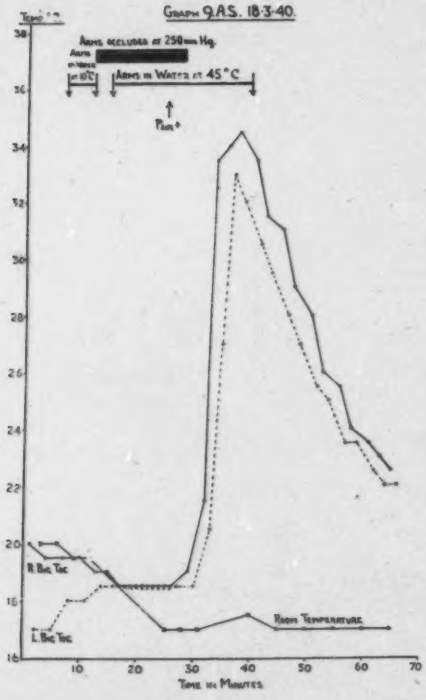
At this stage it will be useful to summarize the data already presented.

In eight experiments performed on seven healthy young adults the findings were as follows :—

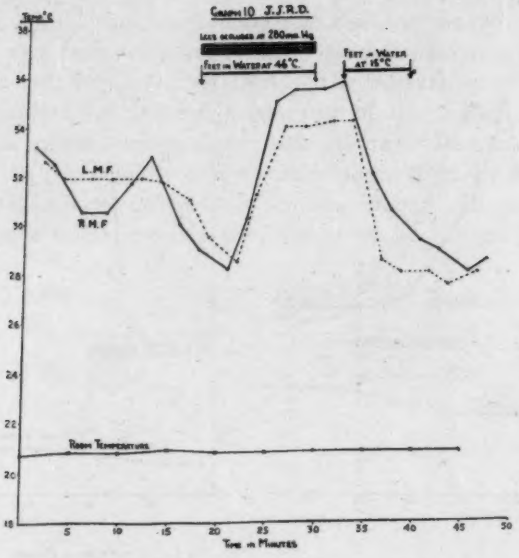
(1) In six experiments heating of the occluded *arms* did not lead to vasodilatation in the toes.

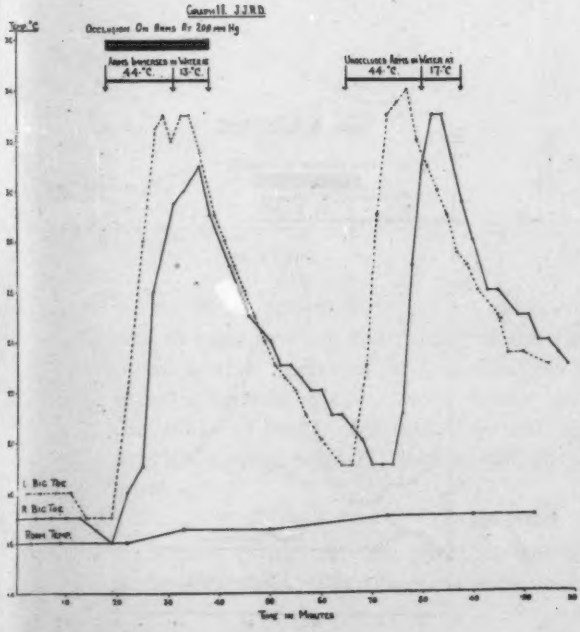
(2) In one experiment heating the occluded legs did not lead to vasodilatation in the fingers.

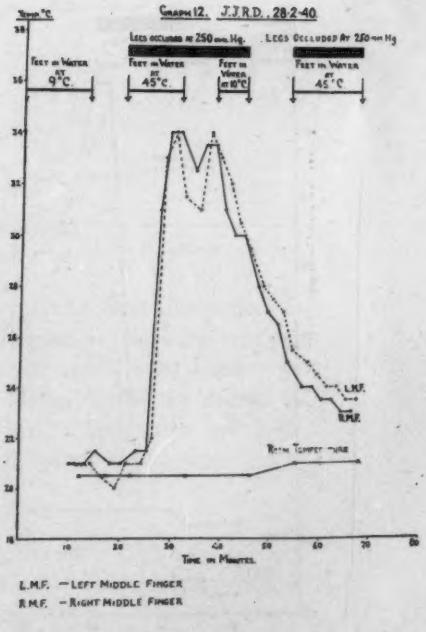
(3) In one experiment vasodilatation occurred in the toes after the occluded arms had been heated for sixteen minutes.

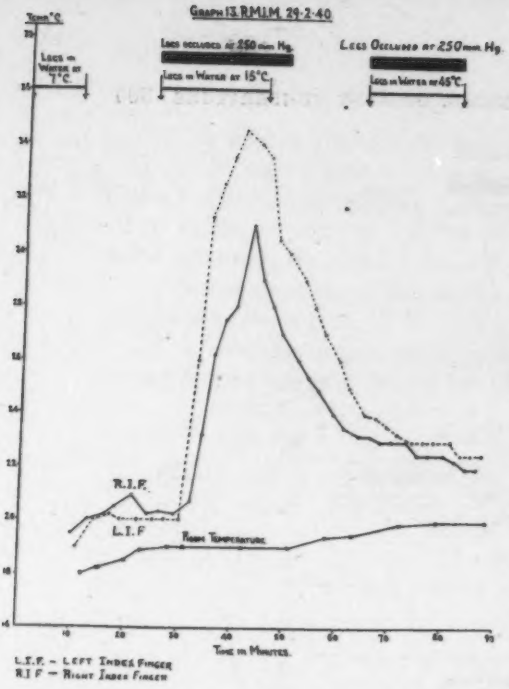


Nine experiments are included in Group 2, seven healthy young adults being used (Graphs 10 to 18). In all but two of these experiments the limbs to be heated were chilled by immersion in cold water before occlusion was applied. In three experiments the occluded arms were heated, and in six the legs. In each of these experiments heating of the occluded limbs for varying periods (nine to twelve minutes) was followed by a rapid rise in the skin temperature of the digits of the unheated limbs. The

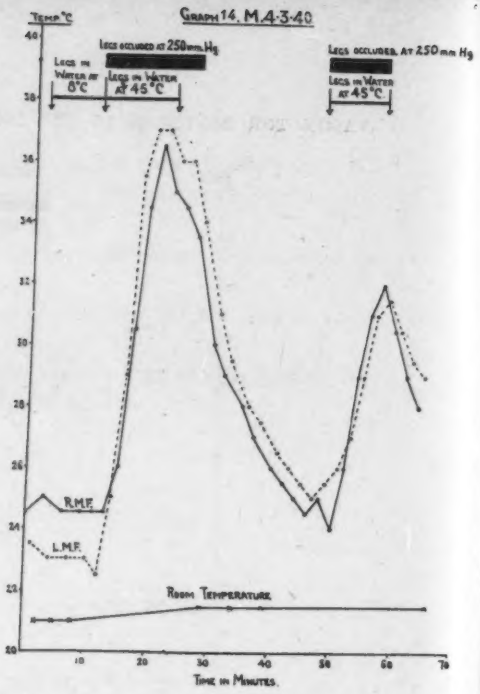

GRAPH 10 J.J.R.D.
LEGS OCCLUDED AT 280mm Hg
FEET IN WATER AT 44°C
FEET IN WATER AT 15°C
L.M.F.
R.M.F.
ROOM TEMPERATURE
TIME IN MINUTES
L.M.F. - LEFT MIDDLE FINGER
R.M.F. - RIGHT MIDDLE FINGER.


GRAPH 11 J.J.R.D.
OCCLUSION ON ARMS AT 200mm Hg
ARMS IMMERSED IN WATER AT 44°C
13°C
UNOCCLUDED ARMS IN WATER AT 44°C
17°C
L. BIG TOE
R. BIG TOE
ROOM TEMPT.
TIME IN MINUTES

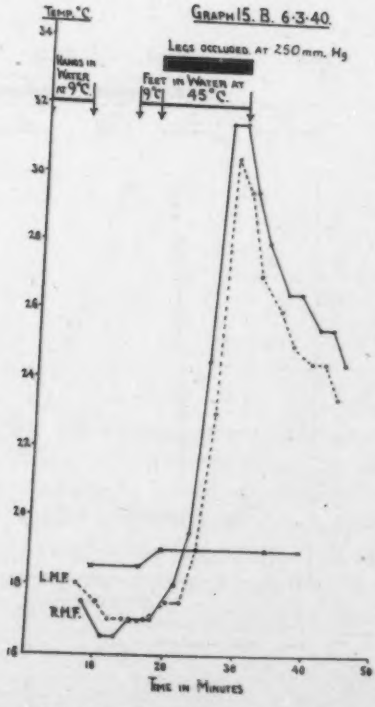

GRAPH 12. J.J.R.D. 28-2-40
LEGS OCCLUDED AT 250mm Hg.
LEGS OCCLUDED AT 250mm Hg
FEET IN WATER AT 9°C
FEET IN WATER AT 45°C
FEET IN WATER AT 18°C
FEET IN WATER AT 45°C
L.M.F.
R.M.F.
ROOM TEMPT.
TIME IN MINUTES.
L.M.F. - LEFT MIDDLE FINGER
R.M.F. - RIGHT MIDDLE FINGER



L.I.F. – Left Index Finger
R.I.F – Right Index Finger



R.M.F. – Right Middle Finger
L.M.F – Left Middle Finger



L.M.F. – Left Middle Finger
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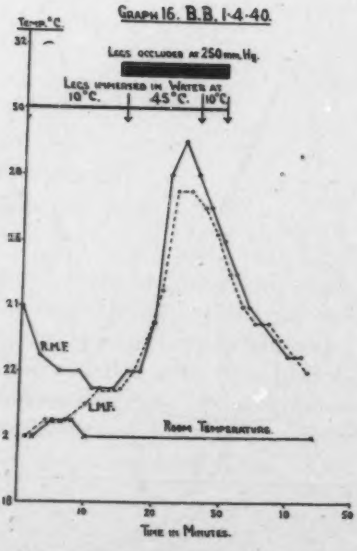
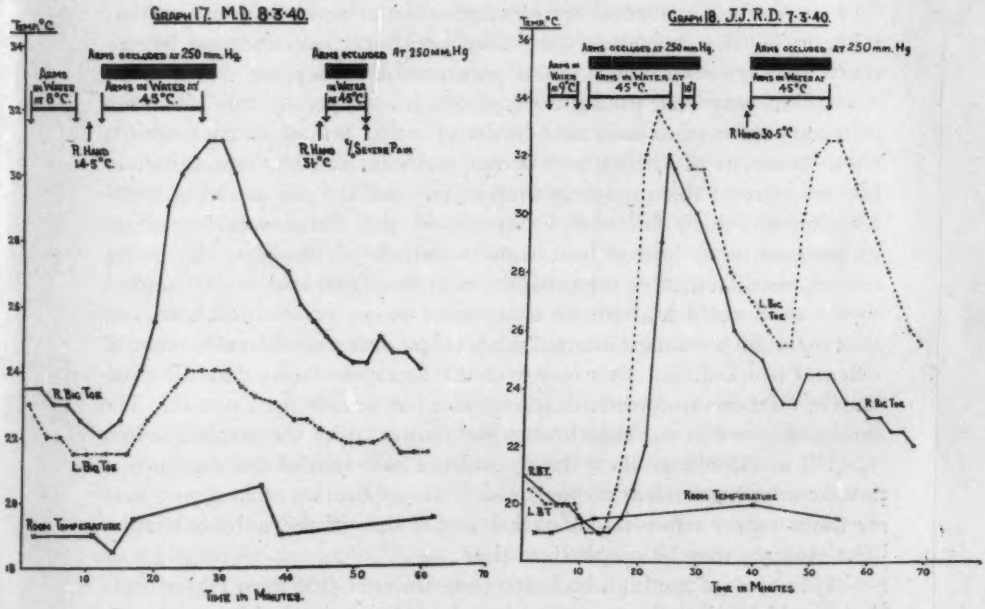


R.M.F – Right Middle Finger
L.M.F – Left Middle Finger

heights to which the skin temperature rose varied in the individual experiments, but with one exception (Graph 16) the maximum temperature recorded was over 30° C. (31° to 37° C.). The interval between the beginning of vasodilatation and the attainment of the highest temperature recorded, was on an average about nine minutes. In four experiments (Graphs 11, 12, 16 and 18) the limbs were removed from the hot water and immersed in cold water before occlusion was released. In each case there followed a rapid fall in the skin temperature of the unheated limbs.



As the arms and legs play an important part in heat dissipation, it was thought possible that arrest of the circulation to the arms or legs might lead to increased heat elimination in the unoccluded limbs. In order to exclude this as a cause of the vasodilatation which occurred in the unheated limbs, occlusion alone was applied to both arms and both legs for varying periods. No vasodilatation occurred in the unoccluded limbs.

Discussion.

In view of the fact that there is abundant evidence that cold applied to the skin causes reflex vasoconstriction in order to conserve heat, it might

be expected that heat applied to the skin would give rise to a corresponding reflex vasodilatation with the same object, the maintenance of a constant internal temperature. The evidence for and against this hypothesis has already been reviewed. Recent work would appear to suggest that application of heat to the skin does not produce reflex vasodilatation, but that the vasodilatation which occurs depends on the warming of the blood and stimulation by it of a thermo-sensitive centre in the hypothalamus. From this it would appear that the maintenance of a constant internal temperature depends partly on a mechanism which is activated by a change in the internal temperature. The evidence for the fact that a rise in blood temperature does cause peripheral vasodilatation has already been reviewed, but it is not unreasonable to suppose that a reflex mechanism may exist the function of which is to prevent any alteration in blood temperature, and thus to act as a first line of defence against rapid variations of environmental temperature. Should these variations become extreme this mechanism might fail, and the rise or fall in blood temperature which followed would act on the thermo-sensitive centre to produce more intense heat conservation or elimination. By reflex control vasodilatation or vasoconstriction arising from heat or cold applied to the skin would lead to the elimination or conservation of heat, and thus maintain a constant internal temperature over a considerable range of external temperature. Our review of the literature shows that the existence of a reflex vasoconstrictor mechanism has already been proved. The results obtained in our experiments and illustrated by the graphs (Graphs 1, 4, 10 to 18) now produce strong evidence in favour of the existence of a vasomotor mechanism through which the application of heat to a limb or limbs causes reflex vasodilatation in the skin of the unheated limbs. The evidence may be summarized thus :—

(1) In view of the high occlusion pressure used (200 mm. Hg or over), heat could not have been conveyed to the general circulation.

(2) A study of the graphs showing vasodilatation occurring on heating occluded limbs (Graphs 10 to 18) reveals the fact that the skin temperature in the unheated limbs began to rise, on an average, after five to seven minutes. About the same interval elapses before distant vasodilatation occurs when unoccluded limbs are heated (Graphs 2, 3 and 4).

(3) When the degree of rise in skin temperature following heating of occluded limbs is compared with that following the heating of unoccluded limbs, it is found that in both cases relatively full vasodilatation occurs.

(4) In Graph 11 it will be seen that there is a marked similarity be-

tween the temperature records obtained from the toes on heating (*a*) the occluded arms, and (*b*) the unoccluded arms.

(5) In Graphs 11, 12, 16 and 18 it has already been pointed out that removal of the occluded limbs from the hot water, and their immersion in cold, caused an immediate and rapid fall in the skin temperature of the unheated limbs. This is in agreement with the results obtained by Pickering (1932) who found that application of cold to an arm, the circulation in which had been arrested, caused conspicuous vasoconstriction in the other arm.

(6) If the occlusion pressures used did not completely arrest the circulation of the heated limbs, another explanation of the vasodilatation occurring in the unheated limbs might be advanced. It has been shown (Lewis, 1927) that heat applied locally gives rise to a vasodilator substance. Were this substance to enter the general circulation in sufficient concentration, some degree of vasodilatation in the unheated limbs might result. That this is not the cause of the vasodilatation observed in our experiments is clearly shown by the fact that release of the circulation of limbs which had been strongly heated had no influence on the skin temperatures of the unheated limbs (*see* Graphs 11, 12, 13, 14, 16 and 18).

The occasional failure of heating an occluded limb to produce vasodilatation in the unheated limbs, calls for comment, and the following points should be considered:—

(1) In five experiments (Graphs 2, 3, 12, 13 and 17) in which the limbs had been heated before occlusion was applied, or where heat was applied to the occluded limbs for a second time, vasodilatation did not occur in the unheated limbs. In these experiments the hyperæmia following the first immersion in hot water had not subsided when the limbs were heated for the second time. Graphs 4 and 13 illustrate the results of experiments performed on the same subject on different days. In the first experiment the arms were heated twice, first unoccluded, then occluded. Vasodilatation appeared in the unheated limbs after the occluded arms had been heated for sixteen minutes. In the second experiment the legs were used and chilled by preliminary immersion in cold water. Vasodilatation appeared in the fingers after eight minutes heating of the occluded legs.

Graphs 5 and 17 also illustrate experiments performed on the same subject. In the first experiment heat applied to the occluded arms for eighteen minutes failed to cause vasodilatation in the toes. In the second experiment where the arms were chilled by immersion in cold water, vasodilatation occurred in the toes after the occluded arms had been heated for six minutes.

It would appear, therefore, that heat applied to occluded limbs whose cutaneous vessels are already dilated, is less likely to cause reflex vasodilatation in distant areas of the skin, than heat applied to occluded limbs in which vasoconstriction of the skin vessels has been induced by preliminary cooling.

(2) When the arms were occluded and heated, no rise in the skin temperature of the toes occurred in six of eleven experiments performed (Graphs 2, 3, 5, 7, 8, 9). When the legs were occluded and heated, in only one experiment of seven performed did vasodilatation fail to occur in the fingers. In most of these experiments, room temperature was below 20° C. Roth, Horton and Sheard (1940) noted that at environmental temperatures below 23° C. the cutaneous vessels of the toes are fully constricted, while those of the fingers may be moderately dilated. This observation was confirmed repeatedly in our own experiments. As has been already stated, heat applied to limbs whose cutaneous vessels are fully constricted is more effective in producing reflex vasodilatation than it is when these vessels are dilated. This would explain the absence of reflex dilatation in Graphs 2 and 3. In the experiments illustrated by Graphs 7, 8 and 9, the arms were chilled by immersion in cold water before heat was applied, but local cold may not induce so powerful a vasoconstriction as is present in the legs at these environmental temperatures.

(3) It was found that on heating the occluded arms, pain was felt early and became intolerable much sooner than was the case when the legs were used.

(4) A study of the Graphs revealed that in those experiments in which vasodilatation failed to appear in the unheated limbs, the room temperatures were, on an average 1° to 2° lower than in those in which vasodilatation did occur.

To sum up, it would appear that heat applied to the occluded legs is more effective in producing reflex vasodilatation than is heat applied to the occluded arms. The fact that pain, which tends to produce vasoconstriction, appears sooner in the arms than in the legs, may partly explain the higher percentage of failures recorded in experiments in which they were used. Response appears to be more certain when vasoconstriction of the skin vessels is present in the limbs before they are heated. Too low a room temperature may provide so powerful a vasoconstrictor stimulus that reflex vasodilatation is inhibited. The failure of previous workers to demonstrate reflex vasodilatation on heating limbs in which the circulation has been arrested, may be accounted for by the action of one or more of these factors. Pickering (1932) stated that vasodilatation as a result of

heating the skin, which has been recently cooled, is only reflex in the sense that it removes the stimulus of cold and its consequent reflex vasoconstriction. Using a calorimetric method of measuring heat elimination from the hand, he found that arrest of the circulation in an arm which was being heated, banishes vasodilatation as measured by heat elimination in the opposite hand, and he concluded that vasodilatation depends not on a reflex, but on warm blood returning from the heated limb. A study of the method employed reveals a possible explanation of the results obtained. The hand from which heat elimination was to be measured was soaked in a tank of water at 30° to 31° C. for ten minues before immersion in the calorimeter. The temperature of the calorimeter during the course of one experiment illustrated, varied between 28·4° and 29·8° C. At these temperatures the cutaneous vessels would be in a state of moderate vasodilatation (skin temperature when the vessels are fully dilated being about 34° to 35° C.). If heat applied to the skin does cause reflex vasodilatation, it must do so largely by inhibition of vasoconstrictor tone. If vasoconstrictor tone has already been partly abolished by immersion of the hand in water at 30° C., it renders the demonstration of its reflex inhibition less likely. If the skin vessels are in a state of moderate dilatation, increase in heat elimination must depend to some extent on an increase in the temperature of the blood flowing through them. The increase in heat elimination from the hand which takes place on heating an unoccluded arm may therefore depend, not on vasodilatation, but on an actual increase in the temperature of the blood. That a slight increase in blood temperature does take place on heating unoccluded limbs has been shown by Uprus, Gaylor and Carmichael (1935) using a rectal thermocouple; and also by Pickering (1932). In our opinion variations in heat elimination of a hand maintained at about 30° C. are not necessarily an accurate index of variations in vasomotor tone. We believe that reflex inhibition of vasoconstrictor tone can best be demonstrated by a rise in skin temperature when the cutaneous vessels have been initially constricted by exposure to low environmental temperatures (17° to 20° C.). This is borne out by the results of our experiments. We have also noted that heating occluded limbs, the skin vessels of which have already been dilated by heat, does not always cause a reflex inhibition of vasoconstrictor tone in the unheated limbs (Graphs 2, 3, 12, 13, and 17). It would appear, therefore, that the afferent impulses may arise, not in the skin itself, but in the cutaneous vessels, and that it is the *active* vasodilatation of these vessels which gives rise to the afferent impulses. Proof that the thermal receptors in the skin are not concerned in this vasometer reflex will be offered in Part II of this communication.

SUMMARY.

A series of experiments were performed on a group of healthy young adults in order to ascertain whether heat applied to one or more limbs during circulatory arrest gives rise to reflex vasodilatation in the unheated limbs. Variations in blood flow to the skin of the fingers and toes were measured by recording changes in skin temperature by means of copper-constantan thermocouples connected to a string galvanometer. Heat was applied to the limbs, occluded and unoccluded, by immersion in water at 45° C. (Landis and Gibbon, 1932).

CONCLUSIONS.

(1) Heat applied to one or more limbs, the circulation of which has been arrested, can in certain circumstances give rise to reflex vasodilatation in the unheated limbs.

(2) It is suggested that the afferent impulses concerned with the production of reflex vasodilatation may arise from stimulation of nerve endings in the walls of the cutaneous blood-vessels.

(3) The hypothesis is advanced that the maintenance of a constant internal temperature may depend upon two mechanisms. Vasomotor reflexes from the skin may compensate for moderate variations in environmental temperature by increasing or decreasing heat elimination from the skin. Should these variations become more extreme, a rise or fall in internal temperature will follow. The change in blood temperature, by its action on thermo-sensitive centres in the hypothalamus, leads to more vigorous conservation or elimination of heat.

PART II.

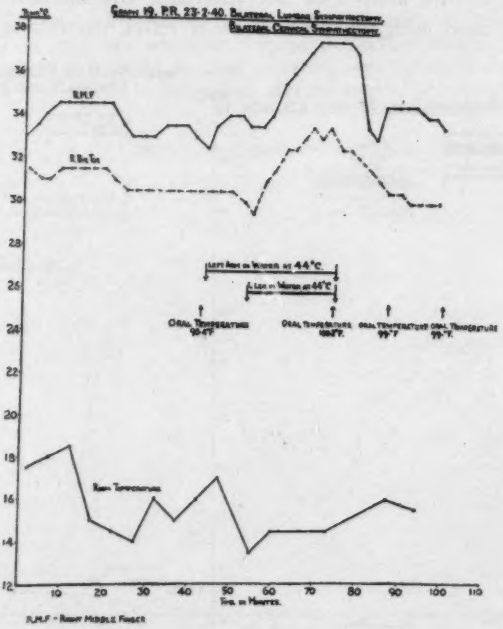
VASCULAR RESPONSES TO WARMING OF PATIENTS WITH VARIOUS NERVE LESIONS, WITH SPECIAL REFERENCE TO AFFERENT PATHWAYS.

In an effort to shed further light on the problem of the vasomotor effects of warming the limbs, a number of patients with various nerve lesions were investigated. The method employed was that described in the first part of this paper.

Case 1.—Graph 19 shows the results of an experiment performed on a young woman in whom bilateral preganglionic lumbar and bilateral preganglionic cervical sympathectomy had been performed for the relief of severe acrocyanosis. The graph shows the variations in skin temperature in the right middle finger and right big toe following immersion of the left arm and left leg in water at 44° C. It will be seen that before heating was started, the skin temperatures indicated that almost full vasodilatation was present in the limbs. As a result of heating an arm and a leg, there was a well-marked rise in the skin temperature of the finger and toe of the other limbs. On removal of the limbs from the hot water, the skin temperatures returned to their previous levels.

In view of the fact that the vasoconstrictor fibres were absent from the limbs, the rise in skin temperature could not be explained by the abolition of vasoconstrictor tone, but may have been due to stimulation of vasodilator fibres running in some pathway other than the sympathetic chain.

It is obvious that heating limbs already fully dilated will rapidly heat the blood. In this case the mouth temperature rose to 100° F. after about

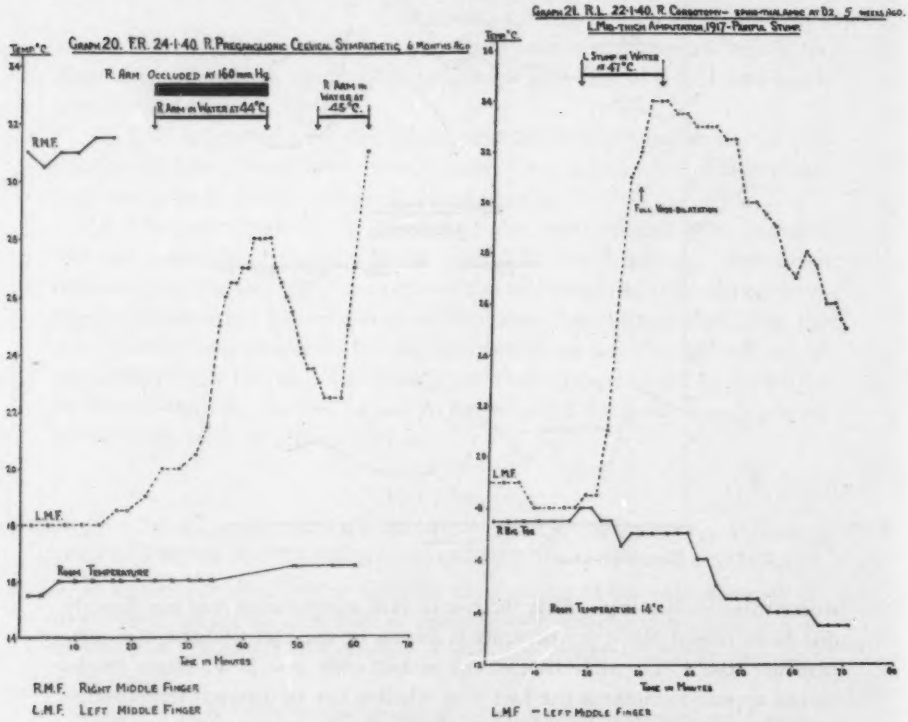


thirty minutes heating. That the rise in skin temperature was not directly due to increased blood temperature is shown by the fact that the skin temperature rose 4° C., while that of the mouth only rose 2° F. These results would appear to confirm the fact that when a rise in internal temperature occurs as a result of heat applied to the limbs, an increase in heat elimination is brought about by active vasodilatation and not merely by inhibition of sympathetic vasoconstrictor tone.

Case 2.—In this experiment the subject was a young woman on whom a right preganglionic cervical sympathectomy had been performed six months previously. Temperature readings were taken from the left middle finger. Occlusion was applied to the right arm, which was then immersed in water at 44° C. After seven minutes heating, the skin temperature of the left middle finger began to rise. In eighteen

minutes it had risen to 28° C. Following removal of the right arm from the water and release of occlusion, a sharp fall in temperature occurred. Re-immersion of the unoccluded right arm in water at 45° C. caused a further and more rapid rise in skin temperature (Graph 20).

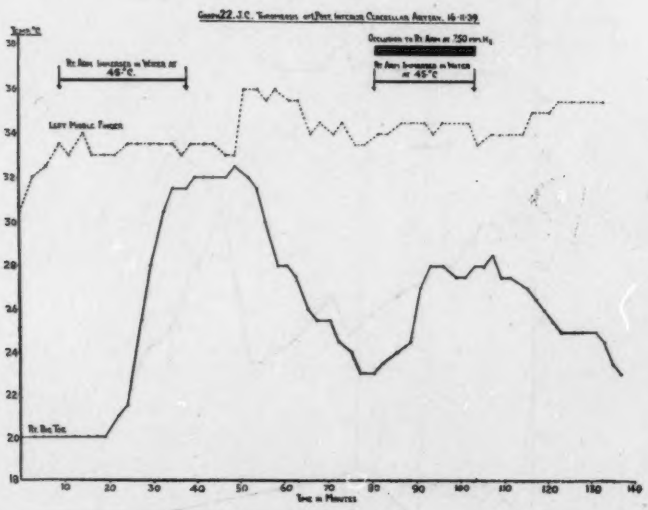
It would appear from this experiment that heating an occluded arm, the sympathetic fibres to which have been cut, can cause reflex vasodilatation in the skin of the opposite hand. Evidently division of the vasoconstrictor fibres to the arm does not interrupt the afferent pathway of impulses concerned with the production of reflex vasodilatation.


Graph 20. F.R. 24-1-40. R. Preganglionic Cervical Sympathetic, 6 Months Ago
R. Arm Occluded at 160 mm. Hg.
R. Arm in Water at 44°C.
R. Arm in Water at 45°C.
R.M.F.
L.M.F.
Room Temperature
Temp. °C.
Time in Minutes
R.M.F. Right Middle Finger
L.M.F. Left Middle Finger
Graph 21. R.L. 22-1-40. R. Cordotomy — spino-thalamic at D2, 5 weeks ago.
L. Mid-thigh Amputation 1917 - Painful Stump.
L. Stump in Water at 47°C.
Vaso-dilatation
L.M.F.
R. Big Toe
Room Temperature 14°C
Temp. °C.
Time in Minutes
L.M.F. — Left Middle Finger

Case 3.—In order to ascertain whether the thermal nerve endings in the skin are concerned in the production of reflex vasodilatation, an experiment was performed on a man in whom the right spinothalamic tract had been divided for the relief of pain in an amputation stump of the left thigh. Examination of the stump showed that there was complete absence of thermal sensation. Temperature readings were taken from the left middle finger (*see* Graph 21). The stump was immersed in water at 47° C. After four minutes heating, rapid vasodilatation occurred in the left finger. Temperature readings from the right big toe showed a progressive cooling throughout the experiment.

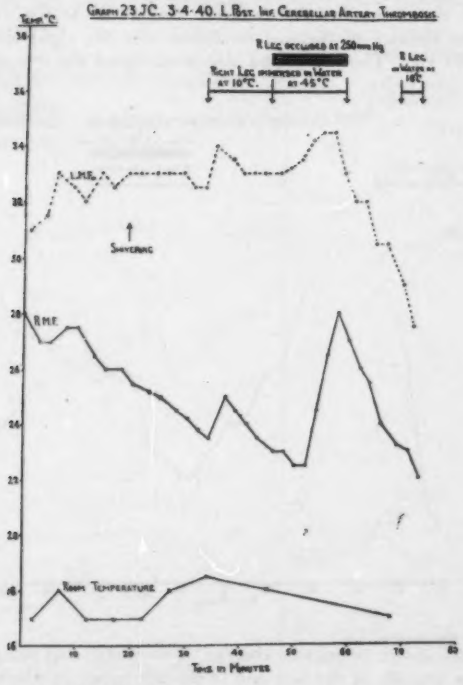
Because of the shortness of the stump, it was impossible to obtain satisfactory arrest of the circulation, so we were unable to observe the result of heating the occluded stump. However, in view of the rapidity with which vasodilatation occurred in the finger, it seems likely that it was the result of reflex activity, but the experiment demonstrates that the afferent impulses from the heated limb cannot run in the spinothalamic tract.

Case 4.—We were fortunate in having the opportunity of investigating a case of thrombosis of the left posterior inferior cerebellar artery. In this patient there was complete absence of thermal sensation over the right side of the trunk, right arm, and right leg. The lesion had also interrupted the sympathetic fibres on



the left side, as was shown by miosis, absence of sweating, and the presence of vasodilatation over the left side of the face and in the left hand, in which the resting skin temperature was 31° to 32° C. Graph 22 illustrates the results obtained in our first experiment. Temperature readings were taken from the right big toe and the left middle finger. The right arm was heated by immersion in water at 45° C. After ten minutes the temperature of the right big toe began to rise. After twenty-seven minutes the skin temperature had risen from 20° to 32° C. Eleven minutes after heating was stopped, a sharp rise in temperature occurred in the left middle finger (33° to 36° C.). The limbs were allowed to cool for forty minutes. The right arm was then occluded and immersed in water at 45° C. After three minutes heating the skin temperature of the right toe again began to rise. In ten minutes it had reached 28° C. Ten minutes after heating was stopped the temperature of the left middle finger again rose 1·5° C. The right toe rapidly cooled after occlusion was released and heating stopped.

The results of this experiment appear to confirm the hypothesis that reflex vasodilatation can result from heating a limb in which thermal sensation is absent, either occluded or not. It should also be noted that a rise in temperature occurred in the finger, the sympathetic fibres to which were presumably interrupted. The delay in the appearance of this rise suggests that it may have been the result of a rise in internal temperature acting centrally. This constitutes further suggestive evidence for the



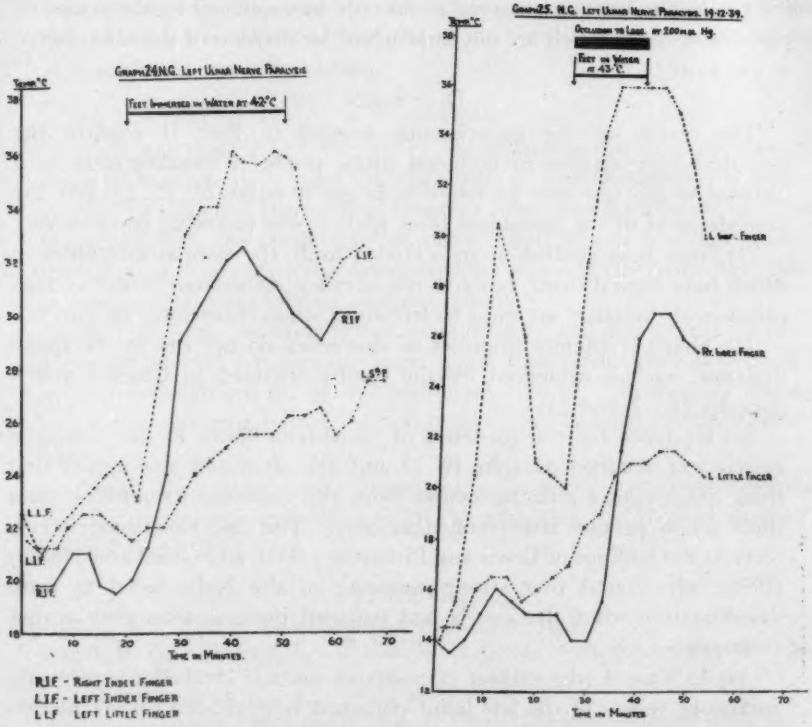
R.M.F. - Right Middle Finger
L.M.F. - Left Middle Finger

existence of vasodilator fibres outside the sympathetic nervous system (*see* Graph 19). The above experiment was repeated after some months had elapsed when similar results were obtained on heating the occluded right leg (Graph 23).

Case 5 was that of a young girl with left ulnar nerve paralysis following traumatic division of the nerve at the level of the wrist. Temperature readings were taken from the left little finger, left index finger, and the right index finger. The legs were immersed in water at 42° C. In twenty minutes the left index finger had risen from

21·5° to 36° C., the right index finger from 20° to 32·5° C., the left little finger from 21·5° to 25° C. (Graph 24). The experiment was repeated with occlusion applied to the legs. After fifteen minutes heating, the temperature of the left index finger had risen from 20° to 36° C., that of the right index finger from 15° to 27° C., that of the little finger from 16° to 21° C. (Graph 25).

The first point to be noted is that there is a marked similarity between the temperature changes resulting from heat applied to (*a*) the unoccluded


Graph 24 N.G. Left Ulnar Nerve Paralysis
Feet immersed in water at 42°C
Temp °C
Time in Minutes
L.I.F.
R.I.F.
L.L.F.
Graph 25. N.G. Left Ulnar Nerve Paralysis. 19-12-39.
Occlusion to Legs at 200 m.m. Hg.
Feet in Water at 43°C.
L. Ind. Finger
Rt. Index Finger
L. Little Finger
R.I.F. - Right Index Finger
L.I.F. - Left Index Finger
L.L.F. Left Little Finger

legs, and (*b*) the occluded legs. This in itself is strong evidence that reflex activity rather than variations in blood temperature is responsible.

Some explanation must be offered for the difference in the degree of vasodilatation occurring in the right and left index fingers in both experiments. It will be seen that the temperature rose several degrees higher in the left finger than in the right on both occasions. One possible explanation is that the sympathetic supply to the vessels of the index fingers comes partly from the ulnar nerve, and that its division at the wrist leads to a

reduction in vasoconstrictor tone. The reason for the rise in skin temperature in the left little finger is rather obscure. It occurred in both experiments, but was less marked in the second, where the occluded limbs were heated. It may be that sympathetic fibres from the median nerve partly supply the skin vessels in the little finger, and that the action of these was inhibited by the application of heat to the legs. On the other hand, if the sympathetic supply to this area of skin runs wholly in the ulnar nerve, the rise in temperature observed could only be explained by the action of vasodilator fibres which are not interrupted by division of the ulnar nerve at the wrist.

Discussion.

The results of the experiments detailed in Part II confirm the fact that heat applied to occluded limbs produces vasodilatation at a distance which can only be reflex in origin (Graphs 20, 22, 23, and 25). Consideration of the individual cases leads to the following conclusions :

(1) Since heat applied to an occluded limb, the sympathetic fibres to which have been divided, can give rise to reflex vasodilatation, the afferent pathway of the reflex arc must be left intact when these fibres are cut.

(2) That the afferent impulses of this reflex do not run in the spinothalamic tract is evidenced by the results obtained in Cases 3 and 4 (Graphs 21, 22 and 23).

(3) Evidence for the existence of vasodilator fibres to the cutaneous vessels was obtained (Graphs 19, 22 and 23). It would also appear that these fibres take a different course from the vasoconstrictor fibres, since their action persists after sympathectomy. This last conclusion is contrary to the findings of Lewis and Pickering (1931), and Grant and Holling (1938), who found that strong warming of the body failed to cause vasodilatation when the vessels had regained intrinsic tone after sympathectomy.

(4) In Case 4 (thrombosis of posterior inferior cerebellar artery), the cutaneous vessels of the left hand remained fully dilated for six months after the lesion occurred. This suggests that the vasoconstrictor fibres were permanently interrupted. The posterior inferior cerebellar artery supplies the medulla oblongata in the region dorsal to the inferior olivary nucleus and lateral to the hypoglossal nucleus. The sympathetic fibres running from the hypothalamus to the lateral horn cells run through this area. These fibres constitute the first neurone of the sympathetic nervous system. The fact that interruption of this neurone is followed by prolonged vasodilatation excludes the possibility of the peripheral ganglia of sympathetic system exerting an autonomous control over the blood-vessels.

SUMMARY.

A number of experiments were performed on patients with various nerve lesions, including division of the preganglionic sympathetic fibres, unilateral division of the spinothalamic tract, thrombosis of the left posterior inferior cerebellar artery, and traumatic division of the ulnar nerve at the wrist. The method used was that described in Part I of this paper. These experiments were planned with the object of obtaining information regarding sensory nerve endings concerned with the production of reflex vasodilatation and the afferent pathway of impulses arising as a result of their stimulation.

CONCLUSIONS.

(1) It has been shown that reflex vasodilatation can take place as the result of heating an occluded limb in which thermal sensation is absent.

(2) The course of the nervous elements conveying the afferent impulses concerned with the production of reflex vasodilatation is unknown, but they remain intact after the vasoconstrictor fibres to the limbs have been interrupted by preganglionic sympathectomy.

(3) The results obtained in two cases (Cases 1 and 4) suggest that when a rise in internal temperature takes place, heat elimination is increased by active vasodilatation of the peripheral vessels. These fibres remain intact after interruption of the sympathetic vasoconstrictor fibres to the limbs.

During the course of this investigation grants were received from the Wilkie Surgical Research Fund (J.J.R.D.), and from the Medical Research Council (R.M.I.M.).

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THE SPINAL COMPLICATIONS OF PAGET'S DISEASE

(*Osteitis Deformans*)

By J. W. ALDREN TURNER

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Although much has been written about the pathology and symptoms of Paget's disease of bone, little attention has been given to the effects the disease may have on the central nervous system. The first authors to describe changes in the spinal cord in a sufferer from the disease were Giles de la Tourette and Marinesco (1894 and 1895) who found degeneration in the posterior columns of the dorsal segments with diminution in the number of nerve fibres and increase in the glial elements in two patients who died of advanced Paget's disease. They thought that these changes were more than a coincidence and suggested that the condition of the bones might be trophic in nature and secondary to lesions in the spinal cord, a condition comparable to the arthropathies of tabes dorsalis. This thesis was supported on inadequate clinical grounds by Pic (1896). The true explanation of these changes in the nervous system was given by Lévi (1897) who showed that they were secondary to periarteritis and endarteritis of the small arteries of the cord resulting in insufficient blood supply, the bone dystrophy and the vascular changes being coincidental in the same patient. This explanation was subsequently verified by Hudelo and Heitz (1901) and by Palmgreen (1927).

During the first twenty-five years of this century a number of cases of Paget's disease complicated by neurological symptoms were reported, but these were practically all cases in which some well-defined neurological condition was present coincidentally with the bone disease, for example tabes dorsalis (Vallery Radot *et al.* (1921); Claude and Oury (1922; Weil and Azoulay (1924); Guillain and Renon (1925)) and syringomyelia (Marie and Léri (1919)).

In 1923 the first real evidence of the production of spinal cord symptoms by Paget's disease was brought forward. In that year Wyllie described two patients with spinal compression caused by osteitis deformans of the vertebræ, one of whom had been relieved by laminectomy. In the same year, independently of Wyllie's observations, a case of paraplegia-in-

flexion accompanying Paget's disease was reported by Ardin-Delteil, Azoulay and Lagrot (1923).

In spite of the recognition for sixteen years that Paget's disease can cause spinal symptoms, surprisingly few cases of the condition have been published, and the more important papers since 1923 have come from France. Reports of four single cases have been published in France (Clovis Vincent, Langeron, Dereux and Lemaître (1936); Petit-Dutaillis, Marchand and Calderon (1936), Haguenau and Sicard (1937) and Garcin, Varay and Dimo (1937)). In England two of my present series have been shown at the Royal Society of Medicine, Case 5 by Brinton (1930-31) and Case 3 by Hunt (1935). Two cases were included in a general review of osteitis deformans by Kay, Simpson and Riddoch (1934) and one has recently been reported by Elkington (1939). A case said to be osteitis deformans causing paraplegia was reported by Morlock (1929-30) but the X-ray reproductions suggest that the disease process was generalized fibro-cystic disease of bone and not osteitis deformans. In America the only case appears to be a rather incomplete account in a general review by Gutman and Kasabach (1936); in Italy one case has been reported by Alessi (1938) and there do not seem to be any reports of cases in the German literature.

No attempt has previously been made to formulate the clinical picture from a study of a group of cases and the results of treatment are relatively unknown.

The cases fall into three groups, which I will consider separately.

A.—Spinal Compression.

There are seven cases of spinal compression in my series, and with these can be grouped the cases of Wyllie, Ardin-Delteil, Vincent, Petit-Dutaillis, and Alessi, making thirteen in all. In analysing them it will be convenient to consider the various features under separate headings.

(1) *Sex and age.*—All my seven patients with spinal compression caused by Paget's disease have been men, and this is true also of the cases reported previously. This is a rather remarkable fact as in series of patients with Paget's disease causing other symptoms, the two sexes are more evenly represented, though males usually predominate; Packard, Steele and Kirkbride (1901) in collecting cases from the literature found 41 males and 24 females and O'Reilly and Race (1932) in a personal series found 24 males and 6 females. It is possible that this undue proportion of men among the cases with spinal compression is a chance finding resulting from the small number of cases observed.

The age of onset of symptoms was usually the middle fifties, though one man had premonitory symptoms when he was 38, and the oldest was 76 before symptoms started. These figures agree with those given for Paget's disease causing other types of symptoms.

(2) *The skeletal evidence of Paget's disease.*—It is not the advanced cases of osteitis deformans which suffer from spinal compression. In not one of my seven cases had the patient been under medical care for deformity or pain in the bones, and only one of them (Case 2) had noticed any previous deformity. In only three was there indisputable evidence of the bone disease in the skull or limbs on clinical examination, and in them the changes were definite but not severe. The bones which appear to show clinical evidence of disease earliest are the clavicles, which become enlarged and roughened and the anterior crest of the tibia which becomes rounded-off and loses its sharp outlines. Usually on radiological examination there is some evidence of Paget's disease in bones other than the spine, but these changes may be minimal and in some cases the disease seems to be limited to the vertebral column, as it may be confined to other single bones in the body, for example the femur (Bowlby 1883). That the disease process was osteitis deformans in the cases which did not show clinical evidence in bones other than the spine has been proved by histological examination of bone removed at operation in three of the four cases in the series.

Clinical examination of the spinal column has usually shown evidence of disease of the vertebræ. Although the marked dorsal kyphosis of the type described by Paget has not been found, two of the seven patients had a moderate degree of mid-dorsal kyphosis without sharp angulation. The most common evidence of disease of the spine in my series has been rigidity and limitation of movement, most marked in the middle dorsal region and seeming to be caused by ankylosis rather than by muscular spasm resulting from pain. In two cases there has been some tenderness over the upper dorsal vertebræ, but this has only been slight in degree; in no case has there been marked tenderness on percussion of the spine.

(3) *The length and type of history.*—My patients have all complained of the neurological symptoms and not of those of the bone disease. Usually the history is of gradual but relentless impairment of the functions of the spinal cord without any remissions. In Petit-Dutaillis' case there was a short period of improvement but this occurred after deep X-ray therapy and was probably attributable to that. The usual length of history before coming to hospital is about twelve months, but Case 1 certainly had symptoms of compression for eleven years and possibly longer, while

in Case 7 the length of history was only five months. Sensory symptoms such as numbness of the legs tend to occur at about the same time as weakness is first noticed, and in all the patients both legs have been involved to about the same degree, a point of some value in the differentiation from spinal neoplasms; as the compression advances, the legs becoming progressively more spastic, sphincter trouble develops and finally flexor spasms and paraplegia-in-flexion result.

(4) *Pain and other sensory symptoms.*—Pain of three different types has been complained of. The first type was pain in the lower part of the back which was worse on movement of the spine; this was an early symptom in Case 1 and was also present in three other patients. In Case 4 this type of pain was a prominent feature and radiated to both buttocks. The cause of this pain is arthritis of the lumbar vertebræ, often with marked osteophyte formation, which is a common accompaniment of osteitis deformans of the lumbar spine. The pain does not differ in character or degree from that complained of by patients with lumbar spondylitis without osteitis deformans.

The second type of pain was the aching in the legs and sometimes in the joints which are a common symptom of Paget's disease, and which were mentioned by Paget in his original description. This was not severe in any of my cases.

The third type of pain which is extremely characteristic is a girdle sensation. This was a prominent complaint in six of my seven patients, and is also mentioned by Wyllie, Alessi and Petit-Dutaillis. Often the sensation was not true pain but was like a band drawn tightly round the trunk, or in one case a burning sensation stretching from the small of the back round the trunk on both sides. The position of the girdle was usually several segments lower than the site of compression, most commonly being at about the level of the umbilicus. Girdle sensations are so common in these cases of Paget's disease with paraplegia, compared with their frequency in cases of spinal neoplasm or indeed of other vertebral causes of compression such as Pott's disease, that there must be some especial reason for them, and I would suggest that they are probably due to narrowing of the intervertebral foramina by new bone formation with resulting gradual compression of the posterior roots as they enter the spinal canal. Root pains of the classical type such as are frequent with spinal neoplasms were uncommon in these cases.

In the later stages of the disease a fourth type of pain usually occurred and that was the pain which accompanied flexor spasms.

Sensory symptoms, apart from pain, were fairly frequent; these were

usually numbness and feelings of cold in the feet which gradually ascended on to the trunk.

(5) *Special features of the compression.*—The outstanding fact about my cases is that in every one of the seven the upper level of compression was at the second, third or fourth thoracic vertebra. When the published cases are studied the same is found to be true with the exception of Haguenau and Sicard's, where the upper level was at the fifth thoracic vertebra, and Ardin-Delteil's where it appears to have been in the lumbar region. This fact seems to me to be a most important one and on looking at the X-ray pictures the reason is apparent, as, although the whole vertebral column may be affected by Paget's disease, the maximum incidence is invariably on the upper thoracic vertebræ.

The upper level of sensory impairment was usually not a sharp one. In a number of the patients there were two levels with two to three dermatomes between them over which the sensory impairment was slight. Even in the cases where only one level was found there was usually a gradual transition from impaired to normal sensation. This fading upper level of sensory impairment is due to the fact that the compression of the spinal cord in Paget's disease is caused by new bone formation in several vertebræ and there is no sharp level of compression such as occurs in many but not all cases of spinal neoplasms.

Local muscular wasting at the level of compression might be expected as a result of narrowing of the intervertebral foramina, but it has not been a feature of any of my cases : this is probably due to the difficulty of detecting local wasting of the intercostal muscles. In a number of the cases there has been paralysis of the intercostals on both sides below the level of the compression together with weakness of the anterior abdominal muscles.

The knee and ankle jerks were usually increased and the plantar responses extensor, but in Cases 2 and 4 the ankle-jerks were diminished. As Case 2 was suffering from diabetes mellitus as well as osteitis deformans it is possible that diabetic neuritis was the cause of the diminution, but this factor was not present in Case 4 and it is likely that vascular changes in the upper sacral segments similar to those described by Hudelo and Heitz (1901) interrupted the reflex arcs.

(6) *Lumbar puncture findings.*—Wyllie (1923) pointed out that in one of his two cases lumbar puncture was impossible as a solid wall of bone prevented the needle entering the theca, and I have had the same experience in three of my cases. This difficulty in lumbar puncture is a diagnostic point of some importance, and should draw attention to the probability

of disease of the vertebral column being a cause of compression, even when this has not been suspected on clinical examination. In the cases where cerebrospinal fluid could be obtained, manometric readings have demonstrated a complete subarachnoid block. The changes in the fluid have been those commonly associated with spinal block from other causes, a rise in the protein content, and sometimes a yellow colour and spontaneous coagulation, but no increase in the number of cells.

(7) *Special diagnostic points.*—In the differential diagnosis the conditions most likely to cause difficulty are an innocent spinal neoplasm and arachnoiditis, as malignant tumours and extradural abscesses usually cause a more rapid destruction of function of the spinal cord, and other causes of spinal compression are most uncommon at the age of fifty or over. The main clinical points to suggest the diagnosis of spinal compression due to osteitis deformans are the presence of changes in other bones, especially the clavicles and tibiæ, the level of compression being at about the third or fourth thoracic vertebra, limitation of extension of the thoracic spine, the presence of severe girdle-sensations usually at a lower level than the compression, and failure of lumbar puncture due to bony obstruction. Another point which may suggest the correct diagnosis is the presence of progressive bilateral deafness which is a common accompaniment of Paget's disease. It is important to remember that the vertebral column may be the only part of the skeleton which is severely affected by the disease.

The radiological appearance of the spine, which is characteristic, will be discussed later, and there is one biochemical estimation of value. Kay (1930) found that the plasma phosphatase content was always raised in osteitis deformans while the blood calcium and phosphorus contents remained unaltered. These findings have been confirmed by others (O'Reilly and Race, 1932) and have been found helpful in the differentiation of Paget's disease from other bone dystrophies.

(8) *Treatment.*—The only treatment which is likely to benefit a patient once a spinal compression has occurred is a decompressive laminectomy. Petit-Dutaillis' case was given deep X-ray therapy which benefited him for a time, but the symptoms recurred and could not be controlled by further irradiation. Six of my patients have had the operation of decompressive laminectomy in the upper dorsal region and the findings in all the cases have been similar. The most conspicuous feature is the considerable increase in thickness of the laminæ, sometimes to as much as three times their normal size; they may also be fused into a bony mass with no demarcation between them. The bone is softer than normal and

is usually vascular; this vascularity makes the operation longer and more difficult than might be expected as the continuous oozing from the cut surfaces of the bone is troublesome to control. Owing to the great increase in thickness of the vertebræ the spinal canal is diminished in size and often no epidural fat is visible. When the dura is first exposed there is no pulsation, but as the decompression is completed pulsation returns.

The most difficult problem is to decide how many laminæ must be removed to relieve the compression which may extend over several segments of the cord. The upper level is usually easy to determine from the clinical findings and the X-ray pictures of the spine, but the lower level is more difficult. Haguenau and Sicard (1937) approached the problem by injecting lipiodol first by the cisternal route and later by the lumbar route and tilting the patient. They found that in their case the compression extended over four vertebræ. This double lipiodol injection has not been employed in any of my patients, though in two cases it was injected by the cisternal route to confirm the upper level of compression. In a number of cases lumbar injection would not be practicable owing to the impossibility of doing a lumbar puncture. If a lumbar lipiodol injection is not done, the lower level can probably be judged best at the time of operation by inspection of the lowest lamina left and of the theca, to see if there is any sign of further compression. It is not necessary to open the dura to secure relief of the compression, but in some cases it may be worth while to do so and to pass a catheter down the subarachnoid space to make sure that the decompression is complete.

(9) *Results of operation.* Owing to the lack of reports of the results of operation on these cases I will consider my series in some detail. In Case 1 the result was an unqualified success; prior to operation there was considerable difficulty in walking, severe girdle sensations and sphincter trouble. Improvement gradually occurred after the laminectomy and has persisted. When the patient was examined three years after operation he was walking perfectly and had no sphincter trouble, his only complaint was of a feeling of tightness round the abdomen. In Case 2 also the result has been most satisfactory. Before operation he was bedridden and had considerable sensory loss and sphincter disturbance; but in spite of prolonged convalescence due to infection of the laminectomy wound, improvement gradually took place and eight months after operation he was walking well with the help of a stick and had no sphincter trouble or girdle pains.

Case 3 has not been so fortunate. Before operation he was bedridden and suffering from frequent painful flexor spasms. After operation there was no return of voluntary power in the legs but the flexor spasms became

much less frequent, normal sphincter control returned, and there was considerable return of sensation. The patient himself was glad that the operation had been performed.

The post-operative course of Case 4 was complicated by severe pain on the right side of the chest, which had the features of a root pain and was not accompanied by physical signs in the chest. Retention of urine occurred after operation, but in the course of eight to ten weeks, normal micturition control returned, and there was considerable decrease of sensory impairment and some improvement in the motor power of the legs.

Case 5 was benefited by operation ; the gait became normal after being spastic and difficult and normal sphincter control returned. He remained well for three years but then the signs of progressive spinal compression recurred and gradually he became bedridden. As he suffered from considerable œdema and cirrhosis of the liver, no further operation was done. Presumably in this case further formation of new bone had abolished the decompressive effect of the laminectomy.

Case 6 developed a complete flaccid paraplegia with profound sensory loss after operation, and he died shortly afterwards of a urinary infection. No operation was performed on Case 7 because of his age and renal condition. He was transferred to an infirmary, where apparently some improvement occurred without special treatment. Unfortunately I have been unable to trace this man since he left the infirmary.

These results show that three cases improved considerably as a result of operation although one of them relapsed some years later ; two cases were moderately improved, and one patient died. They indicate that the operation of decompressive laminectomy is well worth undertaking in cases of spinal compression due to osteitis deformans. A similar conclusion can be drawn from the cases previously reported in which an operation has been performed :—Of Wyllie's patients, one died after operation, but the other improved considerably. Dr. Gordon Holmes tells me that some years later he saw this man, who had developed a sarcoma at the site of the laminectomy. This cannot be regarded as a result of the operation, as the occurrence of sarcoma in patients with Paget's disease is a well recognized complication ; Bird (1927) records seven cases of bone sarcoma amongst a group of sixty-four patients with Paget's disease.

Alessi's patient died shortly after operation, but in the three patients recorded by Clovis Vincent (1936), Petit-Dutaillis (1936) and Haguenau and Sicard (1937), there was considerable improvement, although no record for longer than a few months after operation is available.

The danger of recurrence of compression of the cord by further new bone formation would seem to be real, as demonstrated by Case 5, but I have no further observations of my own as to how often it occurs and can find no reference to it in the literature beyond a remark in a discussion of a case at the Royal Society of Medicine by Julian Taylor (1935) that he had seen a relapse in a patient who had been relieved of symptoms for eight years.

B.—Cases in which a Vascular Basis is Probable.

In both of the cases recorded by Kay, Simpson and Riddoch (1934) the onset of paraplegia was sudden. In one case, a man aged 52, there was dysæsthesia in one leg during the night, followed within a few hours by rapidly increasing weakness of both legs, and within three days he had a complete flaccid paraplegia, anæsthesia to the costal margin and retention of urine. After this there was gradual improvement and five months later there was no sphincter trouble, but he had paraplegia-in-flexion with sensory changes below the fourth lumbar vertebra. The cerebrospinal fluid contained 300 mgm. per cent. of protein and the X-ray pictures of the spine were indicative of Paget's disease. In the second case, a man aged 54, there was a sudden loss of power in both legs while he was walking; he sank to the ground and had to crawl home. After this there was some return of power in the legs. When he was examined three months later his legs were spastic but there was localized wasting and fibrillation in the quadriceps and hamstrings. Lumbar puncture was impossible and there was evidence of Paget's disease on clinical and X-ray examination.

In both these cases the onset of symptoms and the progress afterwards is suggestive of a vascular cause, though it is likely that the vascular accident was secondary to spinal compression, a sequence which is not uncommon in cases of spinal neoplasm, especially if malignant. Operation was proposed to both these patients but was refused.

Elkington's (1939) case was clinically typical of a compression in the upper thoracic region, but lipiodol injected into the cisterna magna descended to the lumbar sac without obstruction, and the author suggested that the case was one of diffuse involvement of the spinal cord with the most intense disturbance in the upper dorsal region; no operation was advised because of the patient's cardiovascular condition.

C.—Case in which there was Vertebral Displacement.

The case described by Garcin, Varay and Dimo (1937) seems to stand alone. A man aged 55 suddenly fell to the ground unconscious; when he

recovered consciousness he had a tetraplegia-in-flexion, so intense in the arms that his clothes had to be cut off. During the next few days power returned in the right arm and leg, and he was found to have a left-sided spinal hemiplegia with sensory impairment over 3rd cervical to 1st thoracic dermatomes on the left and below 4th cervical on the right. X-ray pictures of the cervical spine showed collapse of the body of 4th cervical with displacement backwards of the vertebra. Lumbar puncture gave no evidence of spinal block. There was diffuse decalcification of all the cervical vertebræ. The authors were doubtful about the cause of these changes until they had taken pictures of the skull, which showed characteristic Paget's disease. They thought that the cord symptoms probably resulted from hæmatomyelia secondary to the vertebral displacement, and they emphasized the importance of examining the other bones when X-rays of the spine showed changes of a doubtful nature.

The Radiological Appearances in Paget's Disease of the Spine.

Comparatively little attention has been given to the radiological appearances of osteitis deformans affecting the spine. The study of the pictures in six of my cases helps towards defining the typical X-ray appearances. In the first place the incidence of the disease on the different parts of the spine varies considerably. The cervical vertebræ are seldom affected and when they are, only to a slight degree; the upper thoracic vertebræ, especially 2nd to 5th thoracic, are always maximally involved, while the lower thoracic region is usually involved to a less degree. The lumbar vertebræ show considerable changes but in most cases of a type different from the upper dorsal ones.

The stage of rarefaction has not been a prominent feature, though sometimes there were small scattered areas, chiefly in the lower cervical and the lumbar regions. The most important change has been considerable increase of density and haziness of the outlines of the bones with blurring of detail; for instance the pedicles were not often seen in affected vertebræ. Fusion of three or four of the upper thoracic vertebræ into one bony mass with no demarcation between the constituent bones, has been a conspicuous feature in four of the cases. In the two cases where there was not complete fusion, bridges of bone were seen uniting the lateral parts of the bodies in the antero-posterior view and the fronts of the bodies in the lateral view. The heads of the ribs were usually thickened and blurred in outline, which is an important diagnostic point.

In some cases there was compression of the central parts of the vertebral bodies, for instance in Case 1, 4th and 5th thoracic bodies were compressed.

In this case also there was a deformity of the 11th thoracic body, though this did not seem to be causing symptoms. There was considerable compression of the centre with increase in the width of the body. The lateral view showed that there was some forward displacement of the vertebræ and compression of the posterior part of the body. The anterior part which projected in front of its neighbours was increased in depth and showed pronounced lipping; the density of the bone did not differ from that of the other vertebræ. Rather similar appearances have been reported by Roederer (1936) and by Weismann-Netter and Lasserre (1934).

In the lower lumbar vertebræ the increase in density is usually less uniform and the bones had more of the speckled appearance which is often seen in the skull. There was frequently considerable osteophyte formation. The sacro-iliac joints were usually poorly defined.

There are three conditions in which the radiological appearances in the spine may cause confusion with Paget's disease; Pott's disease, fibro-cystic disease, and carcinomatous metastases. In Pott's disease, the affection is usually limited to a few vertebræ, and the most important evidence in favour of Paget's disease is the presence of changes in a large number of vertebræ. There is usually more deformity of the spine in Pott's disease and thickening and blurred outline of the heads of the ribs is not usual.

In generalized fibro-cystic disease, due to a parathyroid adenoma, there is marked destruction of bone often with cyst formation, but very little new bone production, and in a vertebra the outer part is usually thin with diminished density and often trabeculated in the interior (Snapper, 1936). In this disease all the vertebræ are likely to be affected.

Carcinomatous metastases, especially when these are of the osteosclerotic type associated with carcinoma of the prostate, may give a radiological appearance very hard to distinguish from Paget's disease of the spine. The most important point of distinction is the number of vertebræ affected in Paget's disease, together with the involvement of the ribs and the fused bony mass which is found in a number of the cases.

It is of considerable importance to take pictures of other bones, especially the pelvis, skull and tibiæ in cases where the radiological appearances of the spine are suggestive of, but not typically those of Paget's disease, in the hope of finding evidence of the disease in other parts of the skeleton.

Even if no changes can be demonstrated in the skull or long bones, the abnormal appearance of the vertebral column may still be due to osteitis deformans, as the disease may be limited to the bones of the spine, at any rate in its early stages.

Pathogenesis of the Spinal Complications of Paget's Disease.

Schmorl (1932) has studied the anatomical effects of the disease on the vertebral column. He states that deformity of the vertebral bodies is not unusual; this may be a reduction in their height which occurs when the intervertebral discs retain their resilience, or there may be an increase in the antero-posterior depth due to periosteal proliferation, only in rare cases is the size of the body increased in all directions. The disease may extend to the intervertebral discs when these are penetrated by blood-vessels and then the bone which replaces the disc is "Paget bone" and several adjacent vertebræ may become fused into a bony mass. Spinal curvature may occur when the whole spine is affected. Often there is lipping of the bodies of the vertebræ with synostosis of the margins at their articular surfaces, and the bone joining the vertebræ may be converted into "Paget bone." In advanced cases the spinal canal may be diminished owing to the enlargement of the bodies and the bone composing the vertebral arches; in addition, further pressure points may arise from the formation of bony excrescences springing from the posterior surface of the bodies and other parts of the wall of the spinal canal.

In the museum of the Royal College of Surgeons there is a specimen (Cat: No. 3826·2) of two adjacent dorsal vertebræ affected with osteitis deformans, which shows these changes well. The vertebræ are increased in size and consist of a coarse cancellous tissue, with considerable deposit of bone at the adjacent margins of the vertebral bodies. The laminæ and pedicles also are markedly thickened and as a result the spinal canal has become smaller, and flattened from before backwards. The intervertebral foramina are reduced in size.

When studying a specimen of this type and observing the narrowing and deformity of the spinal canal and intervertebral foramina, it is not difficult to understand why spinal compression and girdle sensations occur. The absence of these symptoms in many cases of osteitis deformans may perhaps be explained by the softness and slow growth of the new bone.

Summary.

(1) Seven personal cases of Paget's disease (osteitis deformans) causing spinal cord symptoms, together with previously reported cases, have been analysed.

(2) The spinal complications associated with Paget's disease fall into three groups, the commonest being spinal compression caused by over-growth of bone and diminution in size of the vertebral canal.

(3) It is emphasized that spinal compression may be the presenting symptom of Paget's disease, the vertebral column being the only bony structure affected by the disease in some cases. The spinal features of this type of compression have been studied.

(4) The operation of decompressive laminectomy is of value in some cases.

I wish to thank Dr. Grainger Stewart, Dr. Gordon Holmes and Dr. Hinds Howell under whose care these patients were admitted to the National Hospital. The subject matter of this paper formed part of a thesis accepted for the degree of D.M. by the University of Oxford.

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Case Histories

Case 1.—*Paget's disease. Spinal compression. Laminectomy D2-4. Symptomatic cure.*

J. B., a man aged 52, was admitted to the National Hospital under the care of Dr. Grainger Stewart on April 6, 1936.

His past and family histories were uneventful.

History of present condition.—About fourteen years before admission he began to suffer from a gnawing pain across the lumbar region which was made worse when he bent forward or turned from side to side. This continued at intervals till about six months before he was seen, when it gradually became less and finally ceased. He had also had a dull heavy pain in the region of the iliac crests for about ten years, which was worse when he was moving about.

During the preceding year he had had periodic feelings of a warm sensation in the lower lumbar region, the front of the knees and the soles of the feet—no precipitating factors for these sensations were known. He had also had burning sensations in the balls of the feet which came on when he was standing up and stopped when he lay down.

For eight months he had had progressive difficulty in walking; he first noticed this when he was going downstairs, and during the two months before admission he had to use a stick for support as he was dragging his legs and was becoming unsteady.

For about five months he had had difficulty with micturition, he had to wait some time before he could pass water and the stream was feeble. There was no incontinence. His bowels had gradually become more constipated.

For four months he had experienced girdle sensations across the back and the abdominal wall above the umbilicus; these felt as if a cord was drawn round his body, and came on when he sat upright but not otherwise.

On examination. Skeletal system.—No abnormality was found in the skull, clavicles or limb bones.

There was no deformity or tenderness of the spine, but the back was held abnormally straight and there was limitation of movement especially in the lower dorsal and lumbar regions.

Nervous system.—There was no abnormality in the cranial nerves or arms.

Motor system.—There was weakness of the lower parts of the recti abdominis. The legs showed no local muscular wasting. There was moderate increase of extensor tone with occasional flexor spasms. Power was markedly diminished at the hips and at the left knee; there was some diminution at the right knee and at the ankles, but relatively less than at the hips.

Reflexes.—The arm-jerks were normal, the upper abdominal reflexes were present, the lower ones absent, the knee and ankle jerks were much exaggerated and the plantar responses extensor.

Sensory system. Superficial.—Below D7 dermatome there was considerable impairment to light touch and complete absence of sensation to pin-prick and temperature. Between D4 and D7 dermatomes there was slight impairment to all these forms of sensation; the upper level was a fading one.

Deep sensation.—Position sense was severely impaired in the toes; many mistakes being made and fine movements of the knees and angles were not appreciated.

Appreciation of vibration was markedly impaired on the iliac crests and on the bony joints of the legs.

Gait was spastic and ataxic, but he was able to walk with a good deal of support.

Cardiovascular system.—No abnormality found.

Investigations.—Lumbar puncture showed an initial pressure of 85 mm.; there was no rise of pressure on bilateral jugular compression, but a free rise on coughing and on abdominal pressure. Only 2 c.c. of fluid could be obtained; this was yellow but did not clot. There was 1 cell per c.mm. The protein was 4,800 mgm. per cent. Wassermann reaction was negative.

Lipiodol was injected by cisternal puncture and was held up at the upper border of D2 body.

Blood calcium was 10·4 mgm. per cent.

Blood-phosphorus was 4·1 mgm. per cent.

Phosphatase was 54 units (normal 8 to 10 units).

X-rays. Spine.—The cervical vertebræ are practically normal, and the 1st dorsal vertebra shows only minimal changes; there is some haziness of its outline and the pedicles are poorly defined. D2-7 vertebræ are fused into one bony mass and there appears to be some compression of the bodies of D4 and 5 from above down. The outline of the vertebræ is hazy and the pedicles and other details are poorly seen. There is considerable increase of density on the left side of D4, 5 and 6 but less increase on the right side and in D2 and 3 vertebræ. There is some thickening of the heads of the ribs.

There is less marked involvement of the lower dorsal vertebræ, but they all show some increase in density and haziness of the outlines of the bodies. The heads of the ribs appear about normal, and the pedicles are well defined in the lower vertebræ.

The 11th dorsal vetrebra is markedly abnormal. In the A—P views it shows compression of the centre of the body and marked increase in the side-to-side width of the vertebra. The sides of the vertebra are less compressed than the centre. The lateral view shows that there is some forward displacement of the whole vertebral body and considerable compression of the posterior part of the body, the anterior part of the body which projects in front of its neighbours is increased in depth and shows pronounced lipping. The density of the bone appears to be much the same as that of its neighbours.

The lumbar and upper part of the sacrum show marked changes. Here there are some areas of increased density and some where the density is diminished. There is "fluffiness" of the outlines of the bones and the pedicles are not visible. There is thickening of the transverse processes of the 3rd lumbar vertebra, and this vertebra is considerably greater in height than the other lumbar vertebræ. The sacro-iliac joints are poorly defined in their upper two-thirds.

Femora are practically normal.

Tibiæ show slight thickening of the cortex, but no other abnormality.

Pelvis.—The bones show patchy areas of increased density and others of rarefaction and the outline of the bones is poorly defined.

During the four weeks after admission the spasticity of the legs became less, but there was considerably increased weakness especially in movements of the hips and knees, and he was only able to hobble along with two sticks. The sensory loss became more marked and pin-prick could not be felt below D4 dermatome and there was some impairment over D3 also.

A diagnosis of Paget's disease affecting the vertebral column and pelvis was made and in view of the progressive compression of the cord in the upper dorsal region, a decompressive laminectomy was advised.

May 12, 1936: Operation was performed by Mr. G. Jefferson. The 2nd, 3rd and 4th dorsal laminæ were removed. There was considerable thickening of the bone which had taken place inwards as well as outwards. The bone was soft, spongy and extremely vascular. There was no distinct line of separation between the

laminæ, so that they formed one continuous sheet of bone. The dura was opened and the spinal cord appeared small. After the laminæ had been removed, a catheter could be passed up and down inside the dura without obstruction and on jugular compression cerebrospinal fluid welled up into the wound. The dura and the wound were then closed. The patient lost about a pint of blood owing to the difficulty in stopping bleeding from the bone.

Histology of bone removed (Dr. Greenfield).—The bone has a very loose structure, the Haversian canals being much enlarged and the bony lamellæ rarefied, so that they occupy in most places a much smaller area than the Haversian canals. The latter are filled with a thin reticular tissue containing osteoclasts. The lines of calcification in the bony lamellæ are very irregular as is also the line of junction between cartilage and bone.

The appearances are those of Paget's disease of bone.

Post-operative progress.—There was gradual improvement after the operation. The girdle pains soon stopped, and though there was occasional incontinence at first, normal sphincter control returned in two to three weeks. When he was discharged ten weeks after operation he was walking slowly with the aid of one stick and there were no further pains. On examination there was still slight weakness at the hips and knees, more marked in the left leg than in the right; but there had been considerable improvement from his pre-operative condition. The upper abdominal reflexes were present and the lower ones absent, the knees and ankle jerks were still increased and the plantars were indefinite extensors. There had been considerable return of sensation; there was moderate impairment to pin-prick and cotton-wool below the groins, more marked on the right than on the left. Position sense was still considerably impaired in the feet and appreciation of vibration was much reduced in the legs.

He was re-examined on March 14, 1939. He was walking normally without a stick, and was at work as a draughtsman. There was rather jerky micturition, but otherwise no sphincter trouble. He suffered from a feeling of tightness round the lower abdomen and in the knees and ankles, but he had no real pain and no numbness.

On examination the only skeletal evidence of Paget's disease was slight increase in width of the tibial crests with rounding off of the sharp edges.

There was some weakness of the lower abdominal muscles. In the legs there was slight wasting of the anterior thigh muscles and of the gluteæ compared with the other muscles. The tone in the legs was normal and the power was very good in all movements of the legs and individual toe movements were possible.

The lower abdominal reflexes were still absent; the knee-jerks were about normal; the ankle-jerks were moderately increased and the plantars were flexor.

The only abnormality of superficial sensation was slight impairment to cotton-wool and pin-prick from D5-L1 dermatomes. Position sense was still absent in the feet and appreciation of vibration was much reduced at the ankles but normal on the iliac crests.

CASE 2.—*Paget's disease. Spinal compression. Laminectomy D2-8. Symptomatic cure. Bilateral deafness. Diabetes mellitus.*

J. R., a man, aged 60, was first admitted under the care of Dr. Gordon Holmes on June 1, 1938.

Past history.—For about twenty years his left arm had been bent, but this was painless and he had taken little notice of it. For about this time also the right leg has been bent and the bone thickened. For many years he had been becoming gradually deaf.

History of present condition.—For two to two and a half years he had noticed a slowly progressive weakness of the legs, so that walking gradually became more difficult. Accompanying the weakness there was numbness in the legs which gradually became more marked. There was no pain, but sometimes he had a feeling of a tight band drawn round his trunk at the level of the umbilicus and sometimes round the thighs also. There was no sphincter trouble and no other symptoms.

On examination. Skeletal system.—The skull appeared larger than normal with some filling out of the temporal fossæ ; the circumference was 23¼ in.

Both clavicles were abnormally large and their surface felt rough. There was some thickening and outward bowing of the left ulna, but the other arm bones felt normal. Both tibiæ were abnormally thickened and their sharp crests were rounded ; there was no definite bowing. The femora felt normal.

Spine.—There was no deformity or tenderness, but the whole spine was held more rigidly than normal and movement of the dorsal spine was limited.

Nervous system.—The cranial nerves were normal, except for bilateral middle-ear deafness.

The arms were normal in motor power, reflexes and sensation.

Motor power.—The intercostal and abdominal muscles were normal.

In the legs there was an increase in extensor tone, and the power was moderately reduced in all movements of the legs, the flexors of the hips and knees and the dorsiflexors of the ankles being more affected than the other muscles.

The abdominal reflexes were present, the knee and ankle jerks were increased and the plantar responses were extensor.

Sensory system. Superficial.—There was very slight impairment to light touch and pin-prick ; the highest level of impairment was between D4 and D6 dermatomes, but the impairment was rather more marked below the umbilicus.

Deep.—Some mistakes in position sense of the toes were made and there was slight impairment of appreciation of vibration on the bony points of the legs.

Gait.—He was able to walk without support, but there was some spasticity and a little unsteadiness.

Cardiovascular system.—The size of the heart was obscured by emphysema. The peripheral arteries were somewhat thickened. Urine normal.

Investigations.—Lumbar puncture gave an initial pressure of 120 mm., but there was no rise of pressure on bilateral jugular compression, although a free rise on abdominal compression. The cerebrospinal fluid was colourless, but a fine coagulum formed on standing. There were 4 lymphocytes per c.mm. and the protein content was 300 mgm. per cent. The Wassermann reaction was negative in blood and cerebrospinal fluid.

X-rays. Spine.—There was slight improvement of the cervical vertebræ, C4 being the most affected. In this vertebra both the body and the lamina were very fluffy in outline and the density of the bone was increased. The body of C6 appeared rather compressed in the centre in the A—P view. All the cervical vertebræ showed some areas of increased density. The spinal canal in the cervical region was clearly defined. D1 was affected similarly to the cervical vertebra, but D2, 3, 4 and 5 were much more extensively involved. In these vertebræ there was considerable increase of density and the outlines of the bodies and the pedicles were very blurred. There was no complete bony union but there was some bony bridging between the lateral parties of the bodies of D2 and 3 and to a lesser extent between D3 and 4. The heads of the ribs showed some increase in thickness and density.

The lower six dorsal vertebræ and the upper two lumbar ones appeared normal except for slight thickening and haziness of the pedicles of L1 and 2.

L3 body showed scattered areas of increased density and others of rarefaction and also blurring of the outline of the pedicles. L4 appeared normal, but in L5 again there were changes similar to those seen in L3.

The sacro-iliac joints were almost indiscernible owing to the blurring of the bony outlines.

The *tibiæ* were both markedly involved—there was considerable thickening of the bones with increase of density and a few scattered areas of diminished density. The medullary canal was not visible in the upper part of the bones but was present in the lower thirds. There was some forward bowing of the right tibia. The fibulæ were not affected.

Radius and ulna (left).—Both showed general increase in density with thickening of the bones and irregularity of the outlines. There was some outward bowing of the ulna. The lower ends were less affected than the upper.

A diagnosis of Paget's disease with early spinal compression in the upper dorsal region was made. No operation was advised at the time and after treatment with massage and exercises he was discharged for further observation.

He was readmitted on March 6, 1939, and said that the weakness of his legs had progressed so much, that during the last month he had been confined to bed; during this time also he had been having painful flexor spasms when his legs were touched. There had been very little pain except with the spasms and sometimes when he changed his position in bed. The tight feelings round his abdomen had become more severe and more frequent. The numbness of the legs had also become more pronounced.

For six weeks he had had increasing difficulty with micturition and at times he had been incontinent of urine. He had lost the sensation of the passage of urine.

On examination there was no change in the *skeletal* condition.

Nervous system. Motor.—There was no contraction of the lower five intercostal muscles and practically no contraction of the abdominal muscles.

In the legs there was marked extensor and adductor spasticity and frequent flexor spasms. All movements of both legs were extremely weak.

The arm reflexes were normal, the abdominal reflexes absent, the knee-jerks were increased but the ankle-jerks were below normal, and the plantars were extensor.

Sensory system. Superficial.—Below D5 dermatome light touches were not felt, the upper level being a gradual one.

Pin-prick and temperature were not felt at all below D11 dermatome and between D5 and D11 there was considerable reduction but not complete loss.

Deep.—Position sense was absent in the legs, and a tuning fork was just felt on the iliac crest, but not on the bony points of the legs.

His urine contained large amounts of sugar, and a fasting blood-sugar was 300 mgm. per cent. Blood urea 41·3 mgm. per cent.

Lumbar puncture again showed a complete subarachnoid block on jugular compression and the cerebrospinal fluid was yellow and contained 600 mgm. per cent. of protein.

It was felt that a decompressive laminectomy should be done, but first his diabetes mellitus had to be controlled. This was done with a diet containing 100 grm. of carbohydrate in twenty-four hours and insulin 20 units in the morning and 5 units in the afternoon.

During the three weeks before operation on this treatment there was some definite improvement, his general condition became better and there was also some increase of power in the legs and lessening of spasticity. Reflexes and sensation remained as before. Micturition was difficult and at times he had to be catheterized.

March 31, 1939 : Operation by Mr. Harvey Jackson. A laminectomy of D2—D8 was done, the laminæ were much thickened and the bone was abnormally soft. It was more vascular than normal but less so than in some cases of Paget's disease. There was less epidural fat than normal. The dura was not opened.

Histology of bone removed (Dr. Greenfield).—The bony spicules show the irregular lines of ossification characteristic of Paget's disease. The Haversian canals contain a quantity of loose connective tissue, as well as many large osteoclastic multinuclear cells. The layer of osteoclasts is also more conspicuous than normal.

Post-operative course.—Recovery from operation was delayed because the lower part of the laminectomy wound became infected, but in the course of three to four weeks this healed. There was progressive improvement in the power of his legs and in sphincter control. Six weeks after operation there was considerable power in all movements, and the plantars were doubtful extensors. The sensory level was as before but the degree of impairment was much less marked.

Twelve weeks after operation when he was discharged he was able to walk with considerable support, but there was marked ataxia due to the loss of position sense. The tone of the legs was normal and all movements were of fair power. The abdominal reflexes had all returned, the knee-jerks were normal but the ankle-jerks were still very feeble, the plantars were both flexor. Light touches were felt everywhere and there was only slight impairment to pin-prick below the groins. Appreciation of vibration remained absent in the legs and position sense was very poor in the feet. There was no sphincter disturbance. In answer to a letter on November 20, 1939 (eight months after operation) he stated that he was feeling very well and had no pain of any sort. There was no sphincter trouble, and he was walking practically normally with the aid of a stick.

CASE 3.—*Paget's disease. Spinal compression. Laminectomy D2-5. Moderate improvement.*

H. W., male, aged 60, was admitted under the care of Dr. Grainger Stewart in February, 1935.

His past and family histories were uneventful.

History of present condition.—Four and a half years before admission he noticed the gradual onset of indefinite aching pains in the shoulders and hips which came on when he was tired and would last for several hours at a time. These pains gradually became worse up to the time of admission. About one year after these pains started, he found that his legs were becoming heavy and progressively weaker so that walking was more difficult. In the course of eighteen months walking became so difficult that he had to give up his work, and for the year or so before admission he was unable to walk at all because of the weakness of his legs, and during this time also he noticed weakness of the lower part of the back and of the abdominal muscles.

For about three and a half years he had suffered from a continuous burning sensation which started in the small of the back and radiated round the lower part of the chest in a band about 6 in. wide. This felt " as if he was being held tight by something," and this girdle sensation gradually became worse and often kept him awake at night.

Six months before admission he started to have involuntary jumping of the legs when he was lying in bed and at times spasms of the abdominal muscles which woke him at night. During the five months before he was admitted he had increasing difficulty in micturition and defæcation and on one or two occasions incontinence of fæces after he had taken an aperient.

There was some numbness of the feet and lower parts of the legs, but not of parts higher than this.

On examination. Skeletal system.—No definite abnormality of the skull noticed. Both clavicles were enlarged, the right more markedly than the left. The bones of the arms appeared normal. The right femur showed some thickening of the lower third of the shaft, while the left femur felt normal. Both tibiæ were abnormal, the crests were broad with rounding-off of the sharp anterior borders and there was some general thickening of the bones, but very little actual bowing. There was some thickening of the iliac crests, especially the right one.

Spine.—No deformity or tenderness, but the dorsal spine was held more rigidly than is usual.

Nervous system.—No abnormality in the cranial nerves or arms was found.

Motor system.—There was wasting of the lower seven intercostal muscles on both sides and no contraction of these muscles on respiration. The abdominal muscles were rigid and at intervals would go into a painful spasm.

Legs.—Involuntary flexor spasms occurred repeatedly and were painful. These were usually violent, flexing the thighs on to the abdomen. There was no wasting of the leg muscles, and there was considerable increase of tone, chiefly in the extensors. There was no voluntary power at hips, knees or ankles.

Reflexes.—The arm-jerks were normal, the abdominal reflexes absent, the knee and ankle jerks were very exaggerated and the plantar responses were both extensor.

Sensory system. Superficial.—There was considerable impairment to cotton-wool, pin-prick and temperature over the legs and trunk below D5 dermatome ; the upper level was a fairly sharp one. There was slightly less impairment of sensation over S3-5 dermatomes.

Deep sensation.—Sense of position in the legs was absent, and appreciation of vibration was absent on the bony points of the legs and on the iliac crests. The patient was unable to stand.

Cardiovascular system.—The heart was slightly enlarged, the apex beat being in the 5th space in the mid-clavicular line. The sounds were normal. Blood-pressure 150/90. The peripheral arteries were thickened. No œdema.

Investigations.—Lumbar puncture was attempted, but the theca could not be entered as a solid wall of bone was encountered.

A cisternal puncture was done and lipiodol injected ; this was held up at the level of D2 body.

The blood Wassermann reaction was weakly positive.

X-rays. Spine.—The cervical and first dorsal vertebræ appeared practically normal, their outlines were clear and the pedicles and spinal canal were outlined well.

The vertebræ from D2-D5 were fused into a bony mass of greatly increased density—the outlines of the mass were hazy and the heads of the ribs were thickened and of increased density. The pedicles of the vertebræ and the outline of the spinal canal could not be distinguished.

The lower dorsal vertebræ showed less abnormality than the upper ones ; there was no fusion of their bodies, but the outlines of the bones were more hazy than normal and the bone was of increased density. There were a few areas of lesser density scattered amongst the denser areas. There was no definite involvement of the ribs in the lower dorsal region, but the pedicles of the vertebræ were very difficult to distinguish.

The lower two lumbar vertebræ and the upper part of the sacrum were severely affected, their outlines were blurred and there were areas of increased density and of increased rarefaction in them. The outlines of the sacro-iliac joints were poorly defined.

Skull.—There was some thickening of the bones of the vault of the skull and the

outline of the bones was "fluffy." The foramen magnum seemed to be pushed up into the skull more than normal.

The pelvis and the femoral heads showed areas of increased density and haziness of the outlines of the bones.

A diagnosis of Paget's disease affecting principally the vertebral column was made and as there was evidence of spinal compression in the upper dorsal region, it was decided to perform a laminectomy.

March 8, 1935 : Operation was performed by Mr. Harvey Jackson. The laminæ of D2, 3, 4 and 5 were removed—they were found to be much thickened and the bone was softer in consistency than normal ; the bone was exceedingly vascular and the bleeding was stopped with some difficulty. There was compression of the theca in the upper part of the wound. The dura was opened, but the arachnoid was left closed. Two milky spots of calcification were present in the arachnoid. The wound was then closed.

Post-operative progress.—One week later the flexor spasms had become much less frequent and less severe and he had regained normal sphincter control. There was no return of voluntary power in the legs, but the upper level of sensory impairment was now at D8 dermatome.

There continued to be slight improvement but when he was discharged in August, 1935, the legs remained very spastic but flexor spasms were much less frequent. The only voluntary power in the legs was some movement of the toes of the left foot.

He had begun to have a constant burning pain over D11-L1 dermatomes on the left. There had been a considerable return of sensation ; he was now able to feel the lightest pin-prick everywhere but rather less than normal.

The knee and ankle jerks remained exaggerated and the plantars were still extensor.

He had normal sphincter control.

He was readmitted in May, 1939, under Dr. Grainger Stewart for re-examination.

He stated that there had been no return in voluntary power in the legs since the operation but the flexor spasms had been much relieved and "life seemed to come back into the legs" and this had remained since.

Micturition had been almost normal, except during the preceding few months when he had had a little difficulty in starting micturition, but there had never been complete retention or incontinence.

For the preceding two to three months he had had a good deal of burning pain in the buttocks and the lower abdomen ; this was always present and was not made worse by coughing, straining, or moving.

On examination. Skeletal system.—The skull showed no evidence of Paget's disease. Both clavicles were much thickened and rounded. The arms were normal. The spine was more flattened than normal in the dorsal region, but there was no deformity or tenderness. Both femora were thickened in their lower halves and there was a little forward and outward bowing. The tibiæ had very broad crests with rounding-off of their sharp surfaces ; there was little actual bowing. Both iliac crests were thickened and the chest had a wide subcostal angle with splaying of the lower ribs.

Nervous system.—The cranial nerves and arms were normal and there was no deafness.

Motor system.—There was no contraction of the lower six intercostal muscles. The abdominal muscles were lax and there was slight bulging of the external obliques on straining. In the thighs the anterior tibial muscles were wasted and flabby compared with the other muscles. There was moderate extensor spasticity of

both legs with considerable adductor spasm—flexor spasms were caused by pricking the feet or pinching the calves. There was no voluntary power in the legs except slight movements of the toes.

Reflexes.—Knee and ankle jerks were much increased and the plantar responses were extensor.

Sensory system. Superficial.—There was moderate impairment to cotton-wool, pin-prick and temperature below D7 dermatome, the impairment being more marked below the groins. There was, however, considerable sparing of the sacral segments 2-5. There was no complete loss to any form of superficial sensation. There was a band of hyperalgesia from D5-D7 dermatomes.

Deep sensation.—Position sense was completely absent in the legs and appreciation of vibration was absent on the legs and iliac crests.

He was unable to stand, but got about in a hand-propelled wheel chair.

Cardiovascular system.—The second aortic sound was accentuated and the blood-pressure was 160/100. Lumbar puncture was again unsuccessful owing to bony resistance.

Further X-rays were taken and these showed that the disease had advanced in the last four years.

CASE 4.—*Paget's disease. Spinal compression. Laminectomy D2-6. Moderate improvement. Slight middle-ear deafness.*

A. C., a man, aged 66, was admitted under the care of Dr. Grainger Stewart, on August 3, 1939.

Past history.—About six years before he had fallen and fractured several ribs but there was no other history of injury or illness.

History of present condition.—About eleven months before admission he noticed numbness in the toes of both feet and stiffness of the knees. During the following months the numbness gradually ascended the legs and reached to the trunk so that by the time of admission everything below the costal margin felt numb. At the same time as the numbness progressed he noticed gradually increasing weakness of both legs, the left leg being more affected than the right one. The knees felt very stiff and often let him down and walking became progressively more difficult.

During most of this time he had had pain in the small of the back and in the buttocks. This was a constant dull aching pain which was worse when he walked and better when he rested.

For seven months he had had difficulty in passing his water and this gradually became worse, but there was never complete retention or incontinence. Three months before admission he was admitted to another hospital where a suprapubic cystotomy was done ; this had, however, healed up.

He had not had any pains in the legs or in the chest. He had lost about a stone in weight in the last few months.

On examination. Skeletal system.—The skull, clavicles and limb bones were normal. In the spine there was a gradual mid-dorsal kyphosis without any sharp angulation. There was no tenderness. There was no marked limitation of movement of the lumbar spine but extension of the dorsal spine was impossible.

Nervous system.—The arms and the cranial nerves were normal except for slight middle-ear deafness.

Motor system.—There was generalized weakness of the abdominal muscles.

In the legs there was no local wasting. The tone in the extensors and adductors was moderately increased. The power was moderately reduced in all movements of both legs, proximal and distal muscles being about equally affected.

The arm-jerks were normal, the abdominal reflexes were absent, the knee-jerks

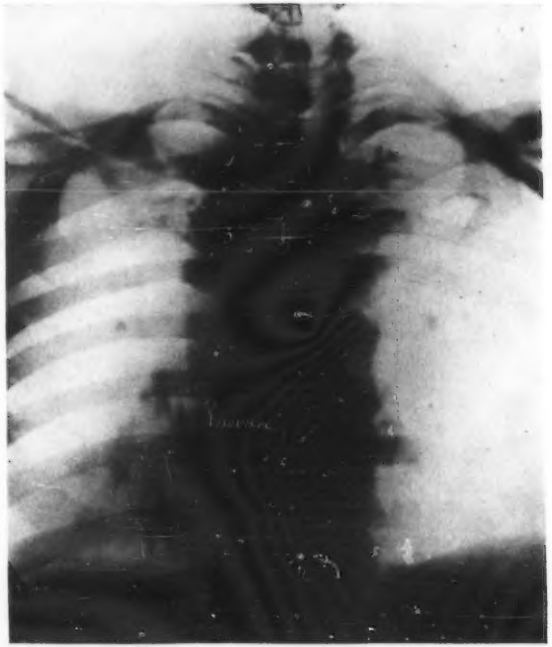

FIG. 1 (*Case 4*).—Upper dorsal spine. A.P. view.—C7 and D1 show slight haziness of the outline of the bodies and increased density and thickening of the pedicles. From D2-8 the bodies of the vertebræ are fused into a single bony mass, there is uniform increase in the density of all these bones with the exception of D2 where the increase is irregularly distributed. The heads of the ribs also show the increase in density to a less degree.

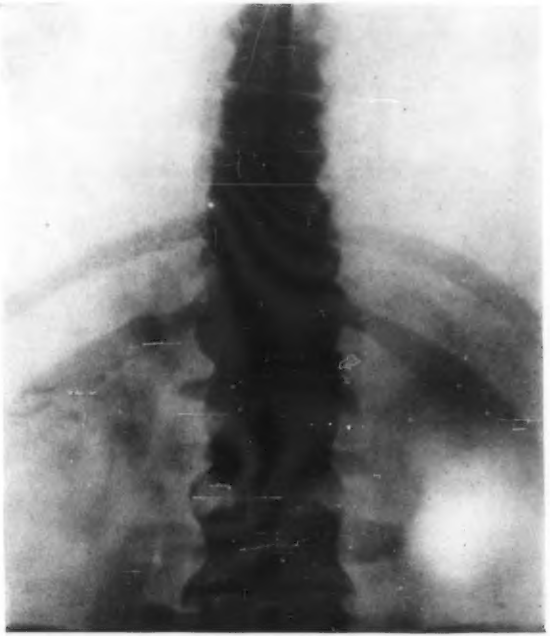

FIG. 2 (*Case 4*).—Lower dorsal spine. A.P. view.—In the lower dorsal spine the density is increased, but less markedly than in D3-8. The outlines of the bones are blurred and the details cannot be distinguished. There is no complete fusion of the bodies but considerable new bone formation in the lateral parts of some of them, resulting in bridges of bone connecting adjacent vertebræ.

were moderately increased, the ankle-jerks were diminished and the plantars were extensor.

Flexor spasms were caused when the soles of the feet were scratched.

Sensory system. Superficial.—Below D6 dermatome there was moderate impairment to cotton-wool and pin-prick and there was slight impairment between D4 and D6 dermatomes ; the level was a soft one.

Deep.—Position sense was considerably impaired in the big toes, and appreciation of vibration was absent at the knees and ankles and much reduced on the iliac crests.

His *gait* was spastic and ataxic, the main difficulty seeming to be the impaired position sense.

Cardiovascular system.—The heart was clinically normal and the peripheral arteries slightly thickened. Blood-pressure 155/70.

Investigations.—Lumbar puncture was unsuccessful, as there seemed to be a solid mass of bone between the lower lumbar vertebræ. At one place there was a small gap and a nerve root was hit but no cerebrospinal fluid was obtained.

The blood Wassermann reaction was negative. Blood urea, 33·4 mgm. per cent.; blood calcium, 9·9 mgm. per cent.; blood phosphorus, 3·8 mgm. per cent.; blood phosphatase, 77·3 units (normal 8-10 units). The urine was infected by *B. coli.*

X-rays. Spine.—C7 and D1 vertebræ show slight changes, these consist of haziness of outline of the bodies, and thickening, increased density and fluffiness of outline of the pedicles. There is some degree of bony fusion between D1 and D2 at the lateral parts of their bodies. The vertebræ from D2 down to about D8 form a bony mass with no proper demarcation between the vertebræ. There is great increase in the density of the bones and haziness of all the outlines. D2 shows some scattered areas of this increased density, but below that the increase is uniform. The heads of the ribs are all thickened and the costovertebral joints are poorly demarcated. The more lateral parts of the ribs appear normal, except the first rib which is uniformly thickened and fluffy.

The dorsal vertebræ below D8 also show greatly increased density, but there is no longer a fused mass of bone, the lateral margins of the vertebræ are, however, joined together by bridges of bone and there is some bridging between the anterior part of the bodies.

The lumbar vertebræ and upper part of the sacrum are also affected ; here the changes in density are more uneven than in the dorsal region. There are some scattered areas of increased density, others where the density is normal or even reduced. There is the same haziness of the outlines of the bones. There is some degree of fusion between the lateral parts of the lumbar vertebræ, and between the fronts of the bodies of L1 and L2 vertebræ. The sacro-iliac joints are poorly defined.

Skull.—There are slight changes indicative of early Paget's disease. There is some thickening of the frontal bones and general slight haziness of the outlines of the bones of the vault.

Right femur and tibiæ.—The lower end of the right femur and the upper end of the right tibia also show slight changes. There is a slight degree of haziness of the outlines of the bone and slight increase in density. The lower part of the right tibia is normal.

Clavicles.—Both clavicles show some generalized increase in density.

A diagnosis of Paget's disease affecting the vertebral column principally was made and as there was evidence of progressive spinal compression in the upper dorsal region, a decompressive laminectomy was advised.

August 16, 1939 : Operation by Mr. Harvey Jackson. A laminectomy from

D2-6 was performed. The laminæ were extremely thick, appearing about three times their normal thickness, the bone was very vascular but seemed harder in consistency than is often found in Paget's disease. The four laminæ which were removed were fused into one mass of bone. There was practically no epidural fat. The dura was exposed, but was not opened.

Histology of bone removed (Dr. Greenfield). Section shows rather thick bony lamellæ in which the lines of ossification are very irregular. These surround fairly large Haversian canals many of which are filled with a loose reticular tissue. Large osteoclastic cells are fairly numerous and many are unusually elongated and flattened against the surface of the bone.

The appearances indicate old-standing Paget's disease of bone.

Post-operative course.—After operation he developed severe and persistent pain on the right side of the chest, which was made worse by straining and by movement; there were no abnormal physical signs in the chest, and in the course of two months the pain gradually became less severe. After operation there was retention of urine and at first the power of the legs was less than before, but after four to six weeks improvement started and slowly continued. When he was examined three months after operation he had regained normal sphincter control and was starting to walk again. The tone of the legs was about normal, but there was still considerable reduction of power especially in the right leg. Appreciation of light touch and pin-prick had improved from his pre-operative state, but a fading level was still present at D6 dermatome. There was no appreciation of vibration in the legs and position sense in the feet was poor. The knee and ankle jerks were present but not increased and the plantar responses were extensor.

CASE 5.—*Paget's disease. Spinal compression. Laminectomy D2-6. Symptomatic cure. Recurrence of symptoms.*

W. B., male, aged 58, was admitted under the care of Dr. Gordon Holmes on January 6, 1930. His past and family histories were uneventful.

History of present condition.—Two years before admission he began to have a constant dull pain in the lower abdomen and a sense of constriction at the level of the umbilicus. The pain and constriction were worse when he moved about; any sudden change of position brought on a sensation of stabbing in the region of the lower ribs on both sides. These pains had been intermittently present up to the time of admission.

Twelve months before admission he began to have slight pains in both legs, especially in the knees, and these pains were worse when he was walking. Six months later the pains extended up to the thighs and to the groins and lower part of the abdomen. At this time also his legs began to feel stiff and were weaker than before. He began to drag them along the ground and at times they gave way, causing him to fall down. The stiffness and weakness gradually became worse so that he had to give up work, and for a short time before admission he was bedridden.

For six months he had had hesitancy and difficulty in starting micturition, and his bowels had become more constipated. On one occasion he had been incontinent of fæces after taking a laxative.

There were no other symptoms.

On examination. Skeletal system.—No definite abnormality was found in the skull or limb bones. There was no deformity of the spine, but there was some tenderness on percussion over D5-7 spines.

Nervous system.—There was no abnormality in the cranial nerves or arms.

Motor system.—There was no contraction of the lower six intercostals and on raising the head the recti abdominis contracted only feebly. There was bulging of the abdominal muscles on coughing.

There was considerable extensor spasticity of both legs, but no local muscular atrophy. The power was considerably reduced in both legs, the weakest movements being extension of the knees and dorsiflexion of the ankles. The arm-jerks were normal, the abdominal reflexes were absent, the knee-jerks were exaggerated, the ankle-jerks were about normal, and the plantar responses were extensor.

Sensory system. Superficial.—There was marked impairment to light touch and pain below D9 dermatome, while between D5 and 9 dermatomes there was slight impairment to these forms of sensation ; the upper level was a fading one.

Deep.—Appreciation of vibration was absent on the bony points of the legs and on the iliac crests, while there was moderate impairment but not absence of sense of position in the toes.

Gait.—He was able to walk in a spastic manner, with considerable difficulty.

Cardiovascular system.—Normal.

Investigations.—Lumbar puncture proved to be impossible on several occasions. The blood Wassermann reaction was negative.

X-rays. Spine.—The cervical and the upper two dorsal vertebræ appear to be normal. From D3-D5 there are definite changes ; there is increase in the density of the bones with haziness of the outlines. There is evidence of fusion between the lateral parts of the bodies of the vertebræ, and in the lateral view some new calcification is seen uniting the anterior parts of the vertebral bodies. No compression of the bodies is seen and no areas of rarefaction. There is only slight thickening of the heads of the ribs.

The lower dorsal vertebræ show less marked changes ; there is, however, some increase in their density and some lipping of the edges of the bodies.

The *skull, femora* and *tibæ* were found to show early signs of Paget's disease.

A diagnosis of Paget's disease with progressive spinal compression in the upper dorsal region was made and a decompressive laminectomy was advised.

January 24, 1930 : Operation by Sir Percy Sargent. A laminectomy of D2-6 was performed, the laminæ was found to be considerably thickened, and the bone was soft and cheesy in consistency. There was marked constriction of the theca due to the bony overgrowth. The dura was not opened.

Histology of bone removed (Dr. Greenfield).—The bone removed shows extreme rarefaction of the bony trabeculæ with fibrous replacement in the Haversian canals, which are greatly enlarged. Many large multinucleated osteoclasts are present in the edges of the larger spaces and in the centre of the smaller spaces. Rows of mononuclear cubical cells line many of the bony trabeculæ. Many large vessels run in the Haversian canals, but it is doubtful if these are more numerous than normal.

The appearances are typical of Paget's disease.

Post-operative course.—There was gradual improvement and when he was discharged twelve weeks after operation he was walking well and his pain and sphincter troubles were largely relieved. There was still slight extensor spasticity of the legs, but there had been considerable improvement in their power. The plantar responses had become flexor. Sensation had also returned to a great extent, it was practically normal on the trunk and in the right leg, but there was still slight impairment to pin-prick over the whole of the left leg.

Later course.—He remained well during the next three years, with no difficulty in walking, but then he tripped and thinks that he hurt his spine. Soon after this fall he began to have pain on the right side of the abdomen and his legs gradually became weaker so that in a short time he had to use two sticks for support when walking.

He was admitted to the Hammersmith L.C.C. Hospital in 1936 and was found

to have well-marked Paget's disease and massive œdema. The cause of this œdema was puzzling, but finally it was thought to be due to cirrhosis of the liver, as on a later occasion he was found to have an enlarged liver and spleen. There was marked spastic paraplegia and impairment of sensation below D9 dermatome. Appreciation of vibration and position were absent in the legs. No further operation was done and the paraplegia has gradually become worse and when last heard of in 1938 he was again bedridden.

CASE 6.—*Paget's disease. Spinal compression. Laminectomy D1-5. Death.*

E. R., a man, aged 46, was admitted under the care of Dr. Collier on October 23, 1934. His past and family histories were uneventful.

History of present condition.—For three years he had noticed numbness of the feet and some unsteadiness of his legs when walking in the dark. The numbness gradually became more marked and during the next twelve months it spread to involve the whole of both legs, and more recently had involved the lower part of the trunk also.

For two years he had noticed gradually increasing weakness of both legs. Within the last few months the weakness had become so severe that he needed the support of two sticks when walking and even then he could only walk a few yards. During these few months also he had had frequent painful flexor spasms, especially when he was just going to sleep.

For two years also he had had a feeling of tightness around the waist. It felt "as if there was a rope pulled tight around the waist." These sensations were brought on by coughing, straining or lifting anything heavy, but in the last few months they were sometimes present without any special precipitating cause. He did not have any other pain.

For three months he had had trouble with micturition, sometimes a difficulty in starting to pass water, and sometimes dribbling incontinence.

There were no other symptoms.

On examination. Skeletal system.—There was slight fulness of the temples, but otherwise the skull was not indicative of Paget's disease.

Both clavicles were grossly enlarged, but the other bones of the arms were normal.

The left tibia showed some thickening and rounding-off of its sharp anterior crest—no definite bowing. No abnormality was found in the other bones of the legs.

The spine showed a slight and gradual mid-dorsal kyphosis but no tenderness. There was limitation of movement of the dorsal spine, but fairly free movement of the lumbar spine.

Nervous system.—The cranial nerves and the arms were normal.

Motor system.—The lower five intercostal muscles did not contract and there was also some generalized weakness of the anterior abdominal muscles. He could not sit up without the support of his arms.

In the legs there was no local wasting, but there was markedly increased tone of the extensor and adductor muscles. The power was grossly impaired, especially in the left leg. He could just raise his legs off the bed against the resistance of gravity. The abdominal reflexes were absent, the knee and ankle jerks were grossly exaggerated and there was bilateral ankle clonus. Both plantar responses were extensor.

Sensory System. Superficial.—Light touch, pin-prick and temperature were markedly impaired below D6 dermatome, the upper level being a fading one.

Deep.—Appreciation of vibration was absent in the legs and on the anterior superior spines. Sense of position was grossly impaired in the feet.

Gait.—Markedly spastic and ataxic, and he needed two sticks for support.

Cardiovascular system.—Blood-pressure was 150/90 and there was slight thickening of the peripheral arteries.

Investigations.—Lumbar puncture showed an initial pressure of 135 mm., there was no rise of pressure on bilateral jugular compression, and only a few drops of fluid were obtained. The fluid was yellow and contained 2,000 mgm. per cent. of protein. There was 1 cell per c.mm. and the Wassermann reaction was negative in the blood and cerebrospinal fluid.

The X-rays were unfortunately no longer available, but the skull, spine, clavicles, pelvis and left tibia were reported to show typical Paget's disease.

A diagnosis of Paget's disease with spinal compression in the upper dorsal region was made and a decompressive laminectomy was advised.

November 13, 1934: Operation by Mr. Harvey Jackson. A laminectomy of the upper five dorsal vertebræ was performed. The laminæ were thickened and the bone was soft and cheesy and extremely vascular, so that there was considerable hæmorrhage which was difficult to check. The theca was exposed but was not opened. The patient was given a blood transfusion after operation.

Post-operative course.—The patient developed a complete flaccid paraplegia with increased sensory loss and retention of urine after operation. He developed a urinary infection and from this he died on January 1, 1934.

Post-mortem by Dr. Greenfield.—The body was that of a wasted man with considerable kyphosis and a well-healed laminectomy wound. The skull was soft, especially over the occipital region, but the bones were not thickened. There was an area of reddish opacity with some roughening on the inner surface reaching across from one temporal ridge to the other just above the occipital protuberance. There was no abnormality of the brain, except perhaps that the cerebellum was unduly small.

The clavicles were thickened and bent, and the tibiæ and fibulæ were thickened and bowed. The lower ends of the femora also looked unduly bent.

The spine was easily cut throughout, especially in the upper dorsal region down to about the tenth dorsal, where the laminæ were thickened and very soft. At the level of the laminectomy the vertebral bodies projected back into the canal on either side of the midline, leaving a central groove. Throughout the dorsal region there was very little space between the bones and the spinal cord.

The cord itself was rather small in the upper thoracic region, but nowhere was it softened. Some of the dorsal roots of the thoracic region were pale and greyish.

The kidneys were both full of small and larger abscesses, which ran up the lines of the tubules to the cortex. The bladder walls were rather thickened and there was offensive pus in the bladder.

The heart, lungs and liver were normal.

CASE 7.—*Paget's disease. Spinal lesion, probably compression. Some degree of spontaneous improvement.*

H. B., a man, aged 77, was admitted under the care of Dr. Hinds Howell on May 20, 1931. His past history was uneventful.

History of present condition.— For about five months he had noticed that his legs were gradually becoming weaker and his gait slow and unsteady. He had fallen down a number of times because of the weakness, and during the preceding month he had needed the support of two sticks when walking. He had also had occasional flexor spasms at night during the last few weeks.

For two months he had episodes of knife-like pain in the middle of his back; this came on especially when he lifted his arms above his head. He also had

frequent feelings of tightness around the upper part of the abdomen, which came on without obvious cause. His legs had felt abnormally cold during this two months.

For a fortnight he had had difficulty in starting to pass his water and there had been occasional incontinence.

There were no other symptoms.

On examination. Skeletal system.—The skull and limb bones showed no abnormality. There was no deformity of the spine, but there was some tenderness on percussion over the 4th and 5th dorsal spines.

Nervous system.—The cranial nerves and arms were normal.

Motor system.—He was unable to sit up without the support of his arms. There was no deviation of the umbilicus and no local bulging of the abdominal wall on straining.

In the legs there was slight wasting of both thighs, relatively to the other muscles. There was moderate increase of extensor tone in both legs, and frequent involuntary flexor spasms. The power in all muscle groups of both legs was slightly reduced, the right leg being rather weaker than the left.

The abdominal reflexes were absent, the knee and ankle jerks were exaggerated and the plantar responses were extensor.

Sensory system. Superficial. Below D6 dermatome pin-prick was not appreciated as pain, and there was subjective impairment to pin-prick also between D4 and D6 dermatomes, the upper level being a fading one. There was impairment to temperature in the same areas and light touch was impaired below D4 dermatome.

Deep.—Appreciation of vibration was absent at the ankles and much impaired on the patellæ and anterior superior spines.

Sense of position was defective in the toes.

Cardiovascular system.—Blood-pressure 130/68. Some thickening of peripheral arteries.

The urine contained pus, albumin and sugar.

Investigations.—Blood urea, 90 mgm. per cent.; fasting blood sugar, 110 mgm. per cent. No lumbar puncture was done.

X-rays. Spine.—The upper cervical vertebræ appeared normal, but C6 and 7 showed areas of increased density and areas of rarefaction in the lateral parts and also general haziness of the outlines of the vertebræ. D1 and D2 showed similar changes but more advanced in degree.

There was some involvement of the dorsal spine from D3 to D6. These vertebræ were fused together into a bony mass and the individual bodies could only be distinguished with difficulty. There was considerable increase in the density especially on the left side of these vertebræ. The outlines were hazy and the pedicles could not be distinguished. There was no definite compression of the bodies. The heads of the ribs were markedly involved, being increased in thickness and their outlines obscure; the costo-vertebral joints were very difficult to distinguish.

The lower dorsal vertebræ were less involved, there was no definite fusion between them, but there was considerable increase of density with obliteration of the pedicles and thickening of the heads of the ribs.

L4 and 5 and the upper part of the sacrum showed changes similar to the lower dorsal vertebræ. The outline of the upper part of the sacrum could not be distinguished and the outlines of the sacro-iliac joints were badly defined.

Skull.—The bones of the vault showed a slight degree of thickening and some

haziness of their outlines, but their involvement was minimal compared with the spine. The sella turcica was normal.

Right femur.—The outline was normal but there was some thickness of the cortex and some irregular areas of increased density.

Clavicles.—These were thickened and on the whole their density was increased, but there were some areas of rarefaction.

A diagnosis of Paget's disease was made, and it was felt that the most likely cause of the spinal symptoms was progressive spinal compression. In view of his age and the renal condition, operation was not advised and the patient was discharged to the Paddington Infirmary.

He was kept there for three months and during this time there was marked improvement in the stiffness and power of the legs and the sphincter trouble became less.

Unfortunately it has been impossible to trace this patient since then.

SUPRAPITUITARY ADAMANTINOMA AND EUNUCHISM.

BY GWENVRON M. GRIFFITHS.

THE association of adamantinomatous or epithelial tumours derived from Rathke's pouch with changes or defects of sexual development is of frequent occurrence, and of the cases reported in the literature a large proportion, though not all, show some degree of sexual change. Analysis of these cases (Duffy, 1920; Critchley and Ironside, 1926; Beckman and Kubie, 1929; Love, Sheldon and Kernohan, 1939) seems to indicate that where there is failure or delay of sexual development or regression (loss of sexual power or cessation of menstruation) the tumour or cystic parts of it involve the base of the 3rd ventricle and the hypothalamic area, while, in other cases, the involvement of this area appears to be slight. But for two cases recently reported by Davison (1940) in which the damage to this region was very great, there seems to have been no detailed examination of the hypothalamic region.

It seems, therefore, worth while to report the findings in two cases, one male and one female, of complete failure of sexual development in patients who reached adult life and worked normally, showing no other symptoms referable to the hypothalamo-hypophyseal complex till very shortly before coming under observation.

Case 1.—F. H., male, aged 24, was the youngest of ten in a healthy working-class family. He had a normal birth and childhood, but was rather spoilt as the baby of the family, being rather childish and preferring to play with children younger than himself. He was rather nervous and a bedwetter. Remaining at school till 14, he was not very bright. After leaving school he worked as a railway porter, earning £2 a week. He lived at home, had a number of friends and a girl friend, and was usually cheerful, but rather quiet.

A year before admission to the Maudsley Hospital he began to have headaches and attacks of vomiting; he became drowsy and lazy. Four months later he was operated upon at St. Thomas's Hospital, where "puncture and aspiration of a suprasellar cyst" was performed. He recovered and resumed work, but limped a little and had occasional cramps in his legs. He began to get fat. He was at this time very thirsty; drank anything he could get hold of and began again to wet the bed. The headaches and vomiting, however, had ceased. For three months he had become slovenly and mentally vague, but continued his work, although on occasions he did not arrive at this but wandered about till night. Consequently he was admitted to the Maudsley Hospital.

Physical examination showed an obese man looking like an overgrown boy—height 4 ft. 10 in., weight 10 st. 10 lb., very pale and unhealthy-looking. The cranial hair was normal; on the face only down was present, and there was neither pubic nor axillary hair. The testicles were very small and retracted into the abdominal ring. The penis was infantile and there was a slight degree of gynæcomastia. The visual acuity was normal; the fundi looked rather pale, but the fields were normal. Physical examination was otherwise negative. Radiograms of the head showed an expanded pituitary fossa with its contents largely calcified, and evidence of high intracranial pressure. The epiphyses of the femur were not joined.

While in hospital he had headaches and vomited at weekly intervals. He was drowsy at certain times; at others noisy. He was careless and slovenly, but mentally clear. He gradually lost weight and died six months later.

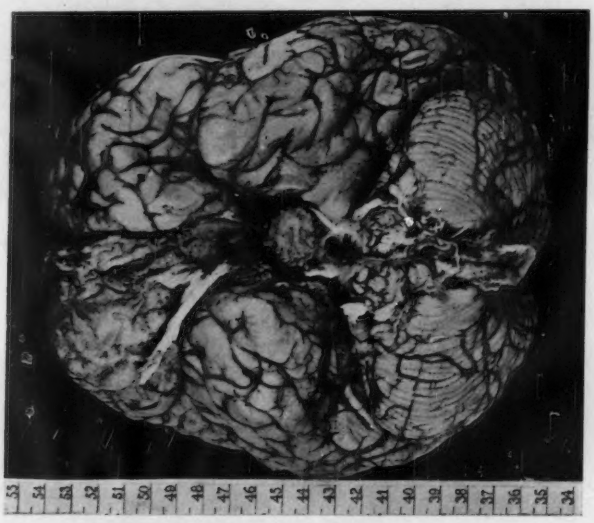

FIG. 1 (*Case 1*).—Base of brain showing the pituitary tumour.

At autopsy, the body was very thin with disproportionately long arms and legs, characteristically eunuchoid in appearance. The bodily organs were healthy, but the endocrine organs were small, especially the testicles.

The head showed the scar of a right frontal osteoplastic flap, and, on removal of the brain, the base of the right frontal lobe was found to be adherent to the dura. Some hæmorrhagic fluid escaped from the adherent region and cystic spaces were found among the adhesions. The sella was exposed and its contents removed with the brain. It was enlarged and flattened, and contained a large solid round mass measuring 2·2 by 1·5 cm. attached to the base of the brain by the pituitary stalk (fig. 1). The optic tracts were thinned over this mass. Under the tip of the left temporal pole presented a large thin-walled cyst which broke, releasing a large quantity of yellowish fluid containing glistening cholesterol crystals (fig. 2). The brain weighed 1,560 grm.

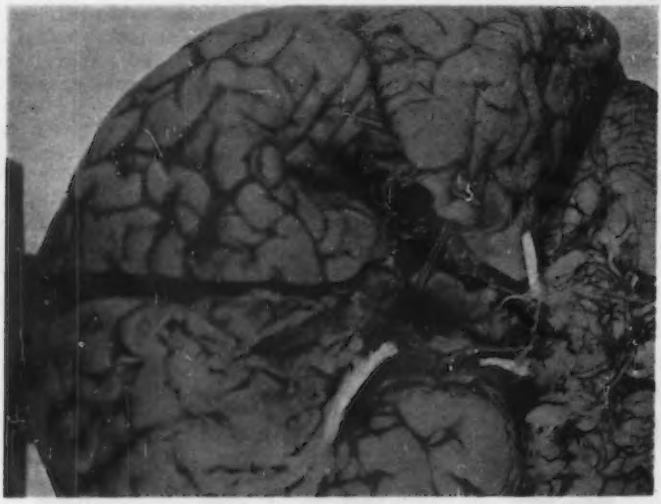

FIG. 2 (*Case 1*).—Base of brain with pituitary removed showing cyst presenting at the tip of the temporal lobe.

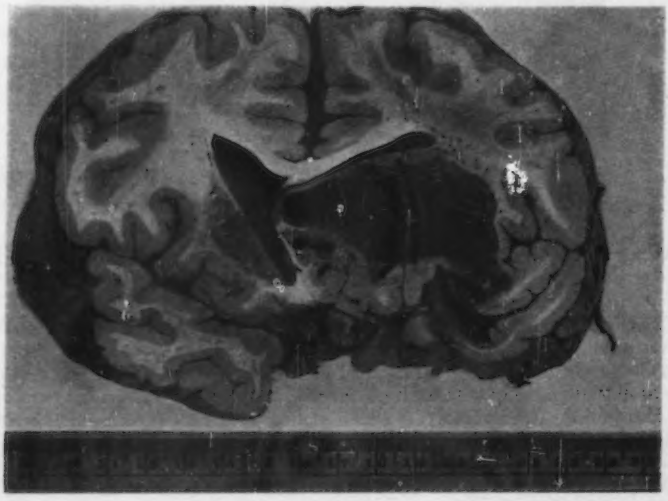

FIG. 3 (*Case 1*).—Vertico-frontal section showing large cholesterol cyst.

On vertico-frontal section the cyst was seen to involve the lower part of the frontal lobe, pushing the 3rd ventricle and septum across the mid-line, but not connecting with the 3rd or lateral ventricles (fig. 3). The cortex and white matter of the anterior part of the frontal lobe were much atrophied, but the cyst did not extend back to the level of the basal gangiia. The anterior part of the temporal lobe was also atrophied. The dimensions of the cyst, after fixing, were 6 by 3 by 8 cm. In the exposed free wall of the cyst was a solid plaque the size of a half-penny.

Microscopic examination of the thyroid gland and thymus showed no abnormality. The suprarenals were small with diminution of thickness of the outer part of the zona fasciculata. The testicles were extremely small, the seminiferous tubules being solid cores of cells in a loose fibrous matrix, with some interstitial cells (fig. 4). No spermatozoa were to be found.

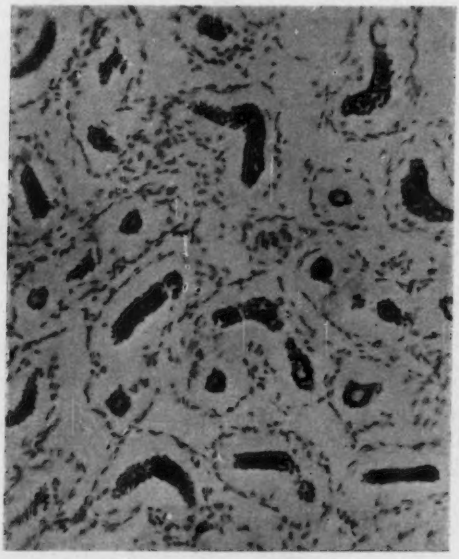

FIG. 4 (*Case 1*).—Testis showing cords of cells replacing seminiferous tubules.

The round mass in the sella was found to consist of tumour of typically adamantinomatous structure, with some degenerated debris in the middle. There was a certain amount of calcification, and some cholesterin clefts were present. On the wall of the tumour in one region was a mass of anterior pituitary substance, slightly compressed, but showing a normal arrangement of sinusoids, acini and cells. The cells were mostly chromophobe, but some were acidophil or basophilic. A mass of colloid was seen in one section. The presence of posterior pituitary substance could not be determined. The pituitary stalk uniting the tumour to the base of the brain showed some fibrous change, and at the upper end was a patch of hyaline material in the middle of the stalk. Sinusoids were absent, and no nerve fibres were to be seen. There was apparently no investment of the stalk with cells of the pars tuberalis.

The infundibular recess was filled with amorphous material, partly fibrous, partly hyaline, containing in some areas cholesterin clefts. There was nothing resembling adamantinomatous tissue in this region. The median eminence behind the recess appeared quite normal.

The plaque on the wall of the cyst showed a solid structure of fibrous trabeculæ containing numerous cholesterin clefts. There were groups of cells containing a dark pigment which gave an iron reaction, and in some places masses of red blood corpuscles lying between the trabeculæ. In other areas were necrotic cells, and in one region a group of pigment-containing octagonal cells.

Serial sections were made through the hypothalamus in a vertico-frontal plane, and stained by hæmatoxylin and van Gieson, hæmatoxylin and eosin, Nissl stain, Mallory's neuroglia stain, Loyez stain for myelin, and by Gros' silver impregnation for unmyelinated fibres. The distortion from both cyst and tumour, however, was so great that in some sections both a vertical and a horizontal picture seemed to be present at the same time, and this made orientation of nuclei and tracts very difficult.

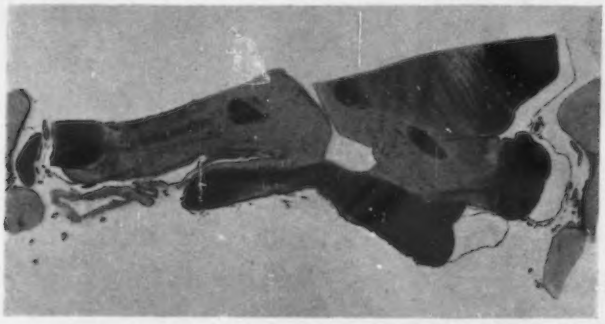

FIG. 5 (*Case 1*).—Vertical section through chiasma. The distortion gives also a horizontal view of the optic tract fibres and internal capsule. The origin of the large cyst is seen between the optic tract and the base of the brain.

Fig. 5, for example, shows a vertical picture of the optic chiasma, as well as a horizontal picture of the optic tracts lateral to the internal capsule. The distortion seemed due in part to the origin of the large cyst, which apparently arose from the region of the base of the brain immediately in front of the pituitary stalk, protruding forward between the base and the left optic tract which was indented by the cyst. The cyst wall was adamantinomatous in this region, though in other parts it consisted of flat epithelial cells. The cyst probably originated in a cell rest at the upper end of the pituitary stalk.

The fibres of the optic tracts appeared to be well myelinated except for a patch ventromedially on the left side. Meynert's commissure was well marked and fornix fibres were fully myelinated (fig. 6). The cavity of the 3rd ventricle was very distorted and on the left side the wall and the base were contiguous from the level of the paraventricular nucleus. The ependyma was irregular, forming in some places deep clefts and in others apparently cysts.

The paraventricular nuclei were quite well marked, though they appeared rounder than is usual in this plane (fig. 7). The cells were widely spaced and

irregular in size, though most of them appeared healthy ; Vacuoles were present in many, but no intracellular colloid was seen. The vascularity of the nucleus appeared to be normal. As the nucleus had been so much stretched in an antero-

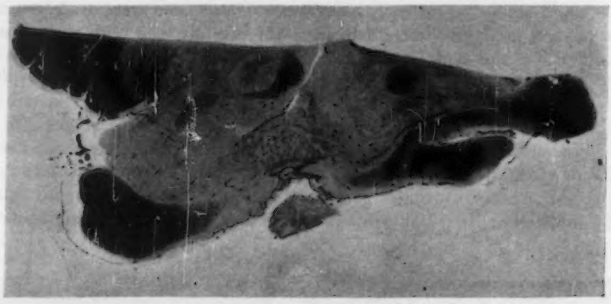

FIG. 6 (*Case I*).—Vertical section showing optic tracts and Meynert's commissure. The right mammillary body appears in a horizontal plane. The infundibulum is filled with amorphous material.

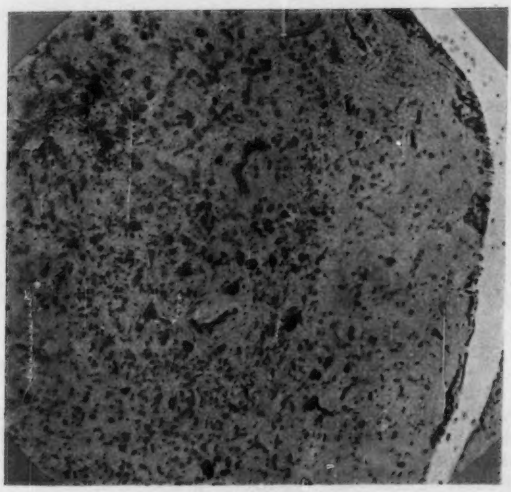

FIG. 7 (*Case I*).—Paraventricular nucleus, showing cells widely spaced, and general roundness of nucleus.

posterior direction it was difficult to estimate the number of cells but it is possible that this was reduced.

On the right side a small number of cells of the shape and size characteristic of healthy supra-optic cells were identified in the position corresponding to the ventro-

medial part of the nucleus (fig. 8). These cells were, as normally, embedded in the superficial glia of this region, which in this case was somewhat increased. The cells showed characteristic vacuolization and appeared perfectly healthy. Representing the usually much larger dorsolateral group were only a few scattered cells, some healthy, but some mere shadows. These cells were widely spaced and not closely packed as in the normal brain. On the left side both groups were very difficult to identify, and consisted of two or three scattered cells, very few of which were healthy. The fibre tracts of this region could not be traced in the silver impregnated sections.

The tuberal nuclei could be readily identified by their peculiar ground substance, and appeared normal in shape and size of cell. The nuclei seemed to retain their individuality among the surrounding distorted tissues. The large well-stained cells of the premammillary group were prominent, though again more widely spaced than normally. The mammillary bodies themselves seemed unaffected.

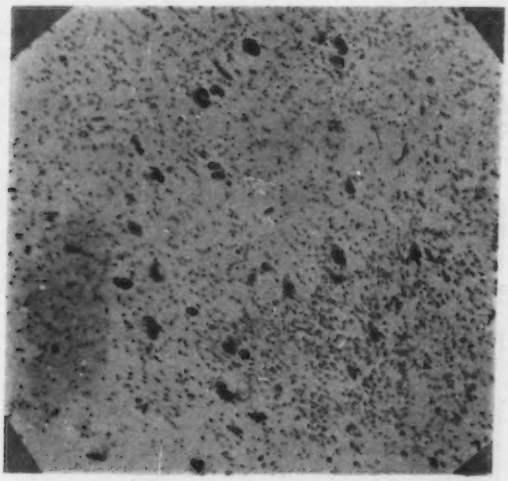

FIG. 8 (*Case 1*).—Supra-optic nucleus, right ventromedial group, a few scattered cells. (Same magnification as fig. 7.)

Case 2.—D. P., female, aged 36, a teacher, was the second of three in a healthy family. She had measles and whooping-cough at 4 years of age; scarlet fever at 13; left mastoiditis at 21 and 25, and "nervous breakdowns" at 11 and 14. She had no physical or emotional changes at puberty, no breast development and no menstruation. She was emotionally neutral and never went to dances or took any interest in the opposite sex. Her whole interest was in her activities as a school-teacher.

She had been in normal health and teaching until, five weeks before her admission to the National Hospital, she had a febrile attack, thought to be a cold, and she lost consciousness for thirty hours. A headache followed but she soon recovered from this. She had noticed that she had been slightly clumsy on occasions, and had bumped into objects without seeing them properly.

On examination she was found to be a fairly tall woman with a pale complexion. Her face was a peculiar round shape with a broad flat nose. The skin was dry and rough. The fingers were short and the hands plump. Apart from the head where hair was normal, there was a complete absence of body hair, the eyebrows were scanty. Secondary sexual characters were undeveloped and infantile in type. The vision was R. $\frac{6}{9}$, L. $\frac{6}{36}$; there was bilateral temporal field defect; the right disc was practically normal, the left disc pale over its whole surface. There were no neurological abnormalities. The heart was enlarged to the right with a mid-diastolic mitral murmur, but no sign of compensatory failure. Cerebrospinal fluid was normal. Radiograms of the skull showed a well-calcified tumour in the pituitary fossa. The epiphyses of the wrist, elbow and knee were not united.

At operation the right optic nerve was found to be stretched over a tumour which bulged up through the prechiasmal space. The tumour capsule was incised and a quantity of soft cheesy white substance removed. She died three weeks later.

FIG. 9 (*Case* 2).—Section through brain showing cyst involving the pituitary and stalk.

At autopsy the body was that of a eunuchoid woman with long limbs and relatively short trunk. The subcutaneous fat was evenly distributed. There were no breasts and no pubic or axillary hair. No blood was found outside the dura, but a large clot escaped from an incision in the frontal lobe. The skull was very thin with digital impressions, and the sutures were closed with membrane only. A cyst covered with firm membrane filled the enlarged sella and interpeduncular space. It was filled partly with blood-clot and partly with more solid tumour (fig. 9). There was much hæmorrhage round the base from the incision in the frontal lobe. The bones of the base of the skull were rarefied.

The thyroid was small and no thymus was visible. The lungs were small; the heart healthy but small. There were marked yellow patches of atheroma in the upper part of the aorta, which was very small. The liver was rather glassy at the

cut surface, and normal in size. The spleen was pale and firm and the kidneys normal. The suprarenals were thin and small, and the uterus and ovaries extremely infantile (fig. 10). On microscopic examination the thyroid showed small vesicles containing colloid, but on the whole it was very cellular. The liver, kidney and spleen showed nothing of note. Sections of the breast showed a few ducts embedded in fat and fibrous tissue, but no gland substance. The ovaries showed a few primordial follicles and a small cyst, but no corpora lutea. The adrenals showed a relative thinness of the outer part of the reticular zone of the cortex.

Serial sections were made through one-half of the base of the brain and tumour and stained in the same manner as in Case 1.

The wall of the tumour showed typical adamantinomatous structure, while the contents were partly blood-clot and degenerated muscle used for hæmostasis, and partly an amorphous substance containing in some places cholesterin clefts. Along the outer wall of the cyst were vesicles of pars tuberalis tissue, in many of which drops of colloid could be seen. This colloid showed the staining reactions characteristic of the intracellular colloid of the hypothalamic nuclei, rather than

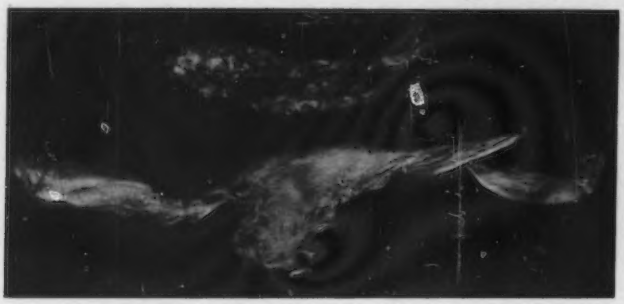

FIG. 10 (*Case* 2).—Uterus and adnexa, and suprarenal.

those of the colloid of the pituitary cleft; this appearance is not uncommonly to be seen in various conditions. At the ventral pole of the cyst was a mass of anterior pituitary substance with mostly chromophobe, but some acidophil and basophil cells. The acini were somewhat compressed, but the sinusoids, though narrow, contained red blood corpuscles. No trace of posterior pituitary tissue could be recognized.

The optic tract and chiasma were stretched over the cyst and thinned considerably, but the fibres were stained fairly well by the myelin stains (fig. 11). Meynert's commissure was well marked. The 3rd ventricle was partially obliterated by the tumour which involved the greater part of the pituitary stalk and anterior aspect of the infundibulum, pushing up the base of the ventricle without invading it, so that the ventricular wall and floor were contiguous to the level of the paraventricular nucleus. The posterior part of the infundibulum was not involved and its structure appeared normal (fig. 12).

The supra-optic nucleus was found to be represented in a few sections by the dorsolateral group only, where the chiasmal fibres reached the base of the brain (fig. 13). The nucleus was elongated and the cells loosely spaced instead of being closely packed as in the normal brain. They were also greatly diminished in

FIG. 11 (*Case 2*).—Section through cyst wall showing its relation with the optic chiasma. The very dark fine line in the wall of the cyst is pars tuberalis tissue. The dark mass in the cyst is blood-clot and degenerated muscle.

FIG. 12 (*Case 2*).—Infundibulum at junction with median eminence showing sinusoids.

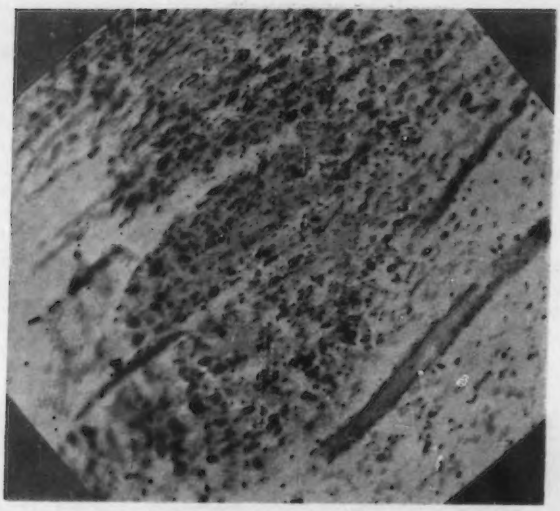

FIG. 13 (*Case* 2).—Supra-optic nucleus, dorsolateral group showing scattering and paucity of cells. (Same magnification as figs. 7 and 8.)

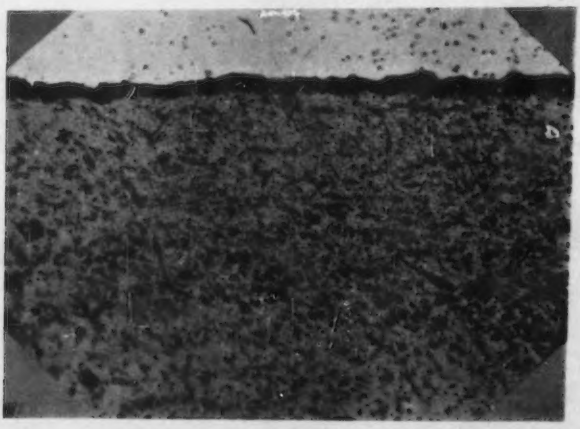

FIG. 14 (*Case* 2).—Paraventricular nucleus relatively normal but cells rather small. (Same magnification as fig. 13.)

number, and while some were healthy, some were shrunken and pale. No colloid was seen in any of them, but a few vacuoles were present. The capillary bed of the nucleus was diminished. The paraventricular nucleus, on the other hand, was relatively unaffected (fig. 14), the cells were numerous, and mostly healthy, many being vacuolated, but again no colloid was found. With silver stains some fibres

of the tract uniting the paraventricular and supra-optic nuclei were seen, but no fibres could be traced into the pituitary stalk, which was entirely involved in tumour. The tumour ended caudally rather abruptly, so that the tuberal nuclei appeared to be quite normal in shape, position and cell content, as were the premammillary nuclei. The mammillary bodies and fornix were entirely unaffected.

Discussion.

In these two cases a completely eunuchoid condition in all ways comparable to that resulting from early castration, was the only symptom till well into adult life, and other symptoms referable to the hypothalamus only appeared towards the end of life. In the first case obesity and thirst followed operative procedure, and the presence of a large cyst involving the frontal lobe may well have accounted for the slight mental symptoms which came on late in the illness. In the second case, visual symptoms from pressure were noticed, and the peculiar attack of unconsciousness may have been hypothalamic in origin.

In both cases the 3rd ventricle was distorted by the tumour, but in neither was there any sign of invasion by tumour of the walls of the ventricle nor of the substance of the base of the brain.

In the first case there were apparently two adamantinomata, one arising from an epithelial rest low down on the pituitary stalk, forming a large intrasellar tumour, and the other, much more cystic, arising from a cell rest at the base of the brain in front of the stalk in the region of the chiasma. In the second case, the tumour involved the whole stalk and the pituitary region, but again rose from the anterior aspect, the posterior aspect of the infundibulum remaining intact.

It is of interest to note that, in both cases, the partial obliteration of the ventricular wall reached as far as but not higher than, the paraventricular nucleus, which thus retained its normal relationship with the ventricular wall, as well as a relatively normal structure.

The striking feature in both cases is the lesion of the supra-optic nucleus. The marked reduction in the number of cells with the preservation of a few apparently healthy cells was apparent in both cases, and cannot be accounted for by pressure, as the adjacent fibres of the optic tract and those of Meynert's commissure were practically intact. In both cases there was a slight excess of gliosis, more than the usual "supporting" glia seen in this area. The capillary network in both cases was much reduced.

The anterior lobe of the pituitary with its characteristic cells and sinusoids was preserved in the wall of the tumour and was probably functioning. Its blood supply seemed adequate judging from the red blood

corpuscles in the sinusoids, though the route may have been abnormal. No tissue resembling pars posterior could be seen, and no certainty of pars intermedia, though a mass of colloid was seen in one section. In Case 2 the whole pituitary stalk was involved in tumour, except at the upper end, where it merged with the caudal aspect of the infundibulum, while in Case 1, the stalk, though macroscopically unaffected, showed fibrous and hyaline changes and absence of sinusoids, again leaving the caudal aspect of the infundibulum and median eminence intact. No nerve fibres (which normally run in the anterior and lateral aspects of the infundibulum) were to be seen. It appears from the anatomical point of view that the supra-optico-hypophyseal complex was peculiarly involved in these two cases, and the condition of the supra-optic nuclei might be interpreted as a retrograde degeneration associated with destruction of the neurohypophysis by the tumour. In support of this view may be cited a case reported by Bini ; a woman, aged 47, who after seven pregnancies (the last associated with eclamptic convulsions) ceased mentruating at the age of 28 and lost her pubic hair, but did not develop obesity or cachexia. The pituitary stalk was mostly replaced by collagenous material with a trace of anterior pituitary substance remaining, but no nervous tissue in the stalk. The supra-optic nucleus was atrophied, having only 8 to 10 cells, but the para-ventricular nucleus was normal. In this case there was thickening of the adventitia of the arteries of the pituitary and supra-optic regions.

A primary destruction of the cells of the supra-optic nucleus as a result of pressure from the tumour is possible, perhaps through vascular compression or other vascular influence, as the capillary network of the nucleus was almost entirely absent. In this connection arise interesting problems. Popa and Fielding postulate a hypophyseal-portal system with continuity of the capillaries of the supra-optic nucleus with the sinusoids and portal vessels of the stalk, with a blood-flow from the pituitary to the hypothalamus. This continuity is denied by Wislocki and others who find the vessels of the stalk to be connected with the infundibulum and median eminence and think the blood-flow is from brain to gland. In these two cases the sinusoids of the stalk are diminished or lacking, but those of the infundibulum and median eminence seem normal. The distortions are so great, however, that the findings cannot be held to confirm or disprove either view.

The presence of colloid in the vesicles of the pars tuberalis in Case 2 is interesting. A similar finding was reported by Duffy in the wall of an adamantinomatous cyst. In this case the patient was an obese man of 35 with genital regression. This colloid appears similar to that sometimes

seen in cells of the supra-optic and paraventricular nuclei though it was absent in both the present cases. The function of this colloid is quite unknown, though it has been suggested that it may pass from the tuberalis cells by the sinusoids of the pituitary stalk into the cerebrospinal fluid at the infundibular recess. In this case such a pathway is conceivably open by means of vessels in the wall of the cyst.

Colloid in the cells of the hypothalamic nuclei is considered by several writers to indicate an endocrine function for these nuclei, and the presence of vacuoles in these cells, which is constant, taken as a phase in the colloid production, though this is scarcely in harmony with the relative paucity of colloid droplets compared with the frequency of the vacuoles. The vacuoles may indicate some other form of functional activity or hormone production. In these two cases a few vacuolated cells were seen in both supra-optic nuclei and many in the paraventricular nuclei ; if they indicate functional activity it is evident that such activity of the supra-optic nuclei was greatly reduced. However there is not as yet sufficient evidence to associate these nuclei with the control of sexual development.

Comparison of these eunuchoid cases with the reported cases of precocious puberty associated with hypothalamic lesions is of interest. In most of these the tumour or mass of ectopic brain tissue has involved the posterior part of this region, the tuber cinereum and mammillary bodies, or has been extracerebrally attached to them. In a personal case, however, a girl of 13 had a tumour lying further forward destroying the infundibulum and median eminence, while the hypothalamic nuclei and mammillary nuclei remained intact.

In Biggart's studies of the hypothalamus in diabetes insipidus, he found destruction of both supra-optic nuclei to be essential for the production of the syndrome, but he also found that involvement of the tuberal nuclei was of still greater importance. He regards the tuberal nuclei as a relay station between the supra-optico-hypophyseal fibres and the mid-brain centres. In the two cases under review the tuberal nuclei were undamaged, and though the supra-optic nuclei showed lesions, they were apparently not sufficiently complete to produce a true diabetes insipidus, though Case 1 showed a tendency in that direction after operation.

It seems from all the evidence that, in these two cases, the primary lesion is that of the neurohypophysis, the damage to the supra-optic nucleus being secondary, either a retrograde degeneration or a result of vascular blocking. There is no definite evidence that the control of sexual development is localized in the supra-optic nucleus.

SUMMARY.

(1) Two cases are reported of a complete eunuchoid condition associated with adamantinoma.

(2) The lesions in the hypothalamic region are detailed and were particularly found in the supra-optic nucleus.

(3) The relative importance of the hypothalamus and neurohypophysis in sexual development are discussed.

I am indebted to the authorities of the Maudsley Hospital for the clinical particulars of Case 1 and to Dr. J. G. Greenfield for advice and help especially with the photomicrographs.

This work was done during tenure of a Kathleen Schlesinger Research Fellowship at the National Hospital.

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PRIMARY DEGENERATION OF THE GRANULAR LAYER OF THE CEREBELLUM: AN UNUSUAL FORM OF FAMILIAL CEREBELLAR ATROPHY OCCURRING IN EARLY LIFE.

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ALTHOUGH the granular cells are commonly involved in processes of atrophy affecting the cerebellar cortex it is unusual to find a distribution of lesions predominantly confined to this layer. Rare examples of this kind have been noted in spino-cerebellar ataxia (Mathieu and Bertrand, 1929) and epilepsy (Scherer, 1931). In general, however, both in focal disease and in the progressive cerebellar degenerations of adult life, atrophy of the granular layer tends to be overshadowed by coincidental Purkinje cell loss. Amaurotic family idiocy in some of the infantile, late infantile and juvenile cases provides the best known examples of clear-cut "cerebellipetal" atrophy (Bielschowsky, 1920). In these conditions it is not uncommon to find widespread reduction in the numbers of granular cells amounting often to complete disappearance and, in addition, destruction of the afferent fibre systems of the cerebellar cortex, the Purkinje cells remaining relatively unaffected save by the lipoid changes characteristic of this group of diseases. The purpose of this paper is to draw attention to a variety of cerebellar atrophy which is unassociated with amaurotic idiocy, is probably congenital in origin, and the distinctive histological feature of which is a selective, widespread and intense degeneration of the granular layer. Schob (1921) who first suggested that this variety of cerebellar disease formed a histologically distinct group cited as examples the third of Vogt and Astwazaturow's (1912) cases of congenital cerebellar anomalies, the case of cerebellar "malformation" described by Deganello and Spangaro (1892) in a dog and Straüssler's (1906) case of a woman of 36 with "congenital cerebellar atrophy." This last, however, was subsequently shown to be an atypical form of amaurotic idiocy (Bielschowsky, Globus, 1923) and thus comes into a different category. To these examples may be added the second of Vogt and Astwazaturow's cases, that of Herringham and Andrewes (1888) which was one of a litter of ataxic kittens and probably Scherer's (1933) case of atrophy of the granular layer in the cere-

bellum of a 22 months' old idiot, though here an element of cerebellifugal atrophy was added in the form of partial demyelinization of the dentate nuclei and the medullary lamellæ. The two familial cases recorded in this paper also belong to this small group of what may be termed "primary atrophy of the granular layer of the cerebellum." Since both occurred in a series of 200 consecutive autopsies carried out in one Colony for mental defectives the condition is probably less rare than the meagre literature of the subject suggests.

Report of Cases.

Case 1.—J. C., a male, aged 11, was admitted to Stoke Park Colony on October 25, 1928.

Family history.—Both parents are alive and in good health (1940); the father, a railway labourer, is 59, the mother 55 years old. The parents were not blood relatives. The patient was the third of seven children. The eldest is healthy but deaf, the second child healthy and normal in every way. The fourth child, a male, died at the age of 13 months from convulsions. The mother stated that up to the day of its death the baby appeared normal. Birth was uneventful and the child was breast fed. There was no suggestion of blindness and the infant had started to walk. The convulsive attacks lasted twelve hours, no other cause of death being discovered. The fifth child, a girl, now aged 13 years, is feeble-minded (Binet-Terman I. Q. 60) and suffers from disease of the nervous system. She suffered from fits in infancy, began to learn to walk at 2 years and speak at 4 years of age. Her articulation remained defective. Dr. Mayhall, school medical officer, kindly supplied me with the following report: "When I saw her first (about eight years ago) she was scarcely able to walk and her speech was hardly understandable. She then suggested a case of cerebellar ataxia—all her muscular efforts were extremely inco-ordinate although mentally she seemed only slightly retarded. As time went on the inco-ordination became less marked, but her mental progress did not continue though she behaved nicely and in an orderly manner. She became able to walk much more freely and took part in ordinary school life, although educationally she was extremely backward. The muscles were then spastic and there was much inco-ordination though less than in her early life. Now there is resistance in arms and legs to all passive movements. There is a localized weakness of muscle and wasting to a slight degree in the left leg from the hip down. There is some inco-ordination resulting in her breaking things when she attempts to put them down, owing to the sudden release of muscular spasm. She is able to knit and perform household duties which do not involve breakages. Mentally she is a nice child of 7 to 8 years."

The sixth child is normal mentally and physically. Dr. Mayhall's visit to the home also brought to light the fact that the youngest member of the family, a boy, aged 9 years, is also feeble-minded and ataxic. He walks with difficulty and speech is very defective. Vision and sphincter control are normal.

Past history.—The records state that mental deficiency was first suspected when the patient was a year old. He did not begin to walk until the age of 5 and his gait remained unsteady. He began to speak at about the same time but articulation was always defective. There was no history of epilepsy.

Examination.—At the age of 13 years 5 months (1930) his Binet-Terman mental age was 3 years 6 months, his Porteous mental age 3 years. He was about 4 years

retarded in physical growth, standing and sitting stature being 128·5 cm. and 70·5 cm. respectively, and weight 30 kilos. With Smedley's dynamometer his right grip was 16 kilos (10th-year level) and his left 18 kilos (12th-year level). His head was small : length 183 mm., breadth 127 mm., height 125 mm. The calculated cubic capacity of the skull was 1,173 c.mm., which approximates to that of the 4th year of life. He suffered from a long standing iritis with secondary cataract in both eyes. Projection of light was fair in the right eye and very poor in the left. The left pupil was fixed ; the right reacted to light save where adherent. Intra-ocular tension was normal and there was no nystagmus. It was impossible to see the fundi. The posture was one of slight general flexion and his gait was ataxic, but he could walk without assistance. Considering his poor vision and low mental grade

FIG. 1. (*Case* 1).—Medial aspect of right hemisphere showing small size of cerebellum and atrophy of the superior vermis.

co-ordination as judged by crude tests did not seem unduly impaired. The arm-jerks were diminished, the knee-jerks exaggerated. The plantar reflexes were flexor. There were involuntary movements in the tongue. Speech was confined to a few words. A year later more obvious neurological signs were noted. There was now marked tremor in the limbs and the knee-jerks were of pendulum type. In 1934 ataxia in arms and legs increased and there was obvious intention tremor. A coarse static tremor was present in the limbs and head. He was still able to walk on a wide base. In 1935 he was able to stand but not walk. He had developed phthisis in 1931, and in 1937, after an attack of influenza, his condition rapidly deteriorated, death occurring in August of that year at the age of 20 years 3 months.

Post-mortem examination.—Both lungs showed chronic cavitating phthisis and there was terminal tuberculous enteritis. The other visceral organs appeared normal or showed mild toxic changes only. The calvaria was thick. The posterior fossa of the skull was small and shelving and the orbital plates excessively domed. The

brain was small, weighing with cerebellum and brain-stem only 853 grm. The meninges appeared normal. After stripping, the cerebral hemispheres showed no gross abnormality apart from their small size, the convolutional pattern being within the range of normal variation. The cerebellum was symetrically and uniformly reduced in size and was obviously abnormally small compared with the brain as a whole (fig. 1)[1]. It weighed with the pons attached 61 grm., and was about the size of a newly-born infant's cerebellum. Its consistence was tough indicating severe sclerosis, and the sulci of the lateral lobes and superior vermis were abnormally widened. The inferior vermis appeared less shrunken. The pons and medulla were of a size consistent with the brain as a whole and appeared massive in comparison with the diminutive cerebellum.

Microscopic examination of the nervous system.—Frozen sections were prepared from representative areas of the cerebral cortex, basal ganglia, cerebellum, brain-stem and upper segments of the cervical spinal cord and stained by standard methods for nerve cells, axis cylinders, myelin, neuroglia and lipoid.

In the *cerebellum* the lateral lobes and superior part of the vermis presented a singularly uniform microscopical appearance, the outstanding feature of which was the complete or almost complete absence of the granular layer (fig. 2). In cresyl violet preparations no distinction could be made out between the central core of white matter of the folium and the area of the cortex subjacent to the Purkinje cell layer, the glial nuclei being equally numerous in both sites. The molecular layer was markedly reduced in depth and contained none of the small nerve cells normally present. In general, the total number of Purkinje cells seemed appropriate for the short, narrow, shrunken gyri and there was widespread heterotopia of these cells in the molecular layer. The cytons of the Purkinje cells stained well and showed no pathological change. They were of fully adult size and seemed unduly large in comparison with the stunted gyri. The heterotopic Purkinje cells, which in many areas formed the majority, showed considerable distortion and variation in shape. These changes were studied in sections stained by Bielschowsky's method and Cajal's nitrate-alcohol-pyridine method. In such preparations the narrow molecular layer seemed crowded with thickened argyrophilic dendritic processes. The Purkinje cells were most frequently of elongated bipolar form, often retort shaped and rarely approximated to the normal antler-like configuration. They were often present in clusters and single cells were commonly seen in the outermost part of the molecular layer. Such cells were unaccompanied by climbing fibres or peri-cellular baskets. Many of the dendrites ended in club-shaped expansions from which fine branches emerged (fig. 3). In many examples these radially placed processes formed an unusually dense brushwork, the whole structure, when seen in a thin section without the accompanying main dendrite, somewhat resembling in appearance a certain variety of senile plaque (figs. 4 and 5).

The axons of the Purkinje cells sometimes pursued a lateral course in a direction parallel with the deeper part of the molecular layer. In many of the heterotopic Purkinje cells the axons could be traced running in the normal way into the central core of white matter. Axonal torpedoes of large size were very numerous (fig. 6). In sections cut at right angles to the course of the folium it was seen that a conspicuous bundle of parallel fibres occupied the lower part of the molecular layer below the level of the heterotopic Purkinje cells. From these parallel fibres short descending branches ran in the direction of the central core, occupying what normally should have been the outer part of the granular layer. These descending

[1] Some other photographs of this brain have appeared in "A Cerebral Atlas," Berry, R.J.A., Oxford University Press, 1938.

FIG. 2.

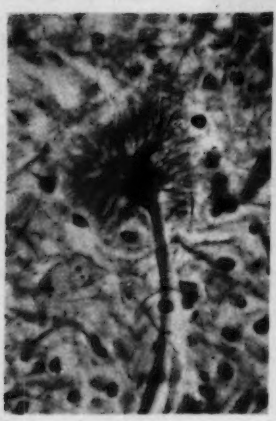

FIG. 4.

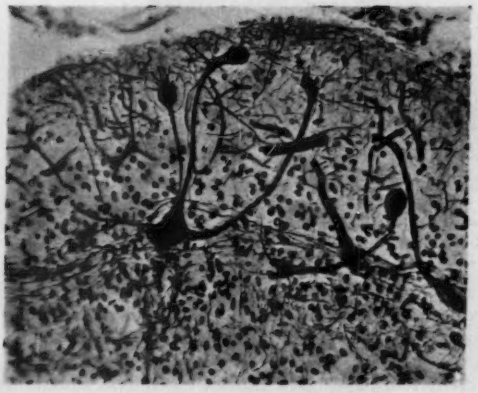

FIG. 3.

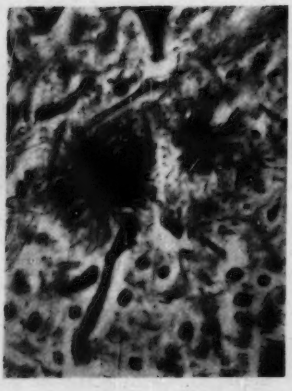

FIG. 5.

FIG. 2. (*Case* 1).—Left posterior quadrangular lobule. Total atrophy of the granular layer. Cresyl violet × 24.

FIG. 3 (*Case* 1).—Left biventral lobule. Cactus-like swellings of the dendrites of a Purkinje cells. Cajal's silver-nitrate-alcohol-pyridine method × 180.

FIGS. 4 and 5. (*Case* 1.)—High power view of dendritic expansions showing dense radial brushwork. Bielschowsky's method × 400.

branches formed a uniformly spaced curtain and localized aggregations in the form of empty pericellular baskets as seen in cerebellofugal atrophy were not observed. In sections cut parallel to the course of the folium the tangential fibres derived from the granular cells were entirely absent.

The white matter of the cerebellum was fully myelinated and considering the total atrophy of the granular cells, the myelinated fibres of this layer showed remarkably little disturbance (fig. 7). When compared with sections taken from a normal adult, however, it was evident that a considerable reduction in the number of fibres had occurred. No demyelinization of the central white matter was seen. Holzer staining revealed a massive fibrillary gliosis of all layers of the cerebellar cortex and of the medullary lamellæ of the folia (fig. 8). In the molecular layer the Bergmann fibrils were thickened and proliferated. The whole of the central white matter was sclerosed. Sections stained by scharlach R showed no abnormal lipoid content in nerve cells, blood-vessels or myelinated fibres. The dendritic expansions of the Purkinje cells contained no lipoid. No compound granular corpuscles were seen.

FIG. 6. (*Case* 1).—Left biventral lobule. Heterotopia of Purkinje cells, absent granular layer, numerous axonal torpedoes. Cajal's silver-nitrate-alcohol-pyridine method × 60.

The macroscopically less shrunken areas of the cerebellum showed in their minute structure less extravagant abnormalities. In the uvula and pyramid the Purkinje cells were of normal shape, possessed pericellular baskets and were regularly arranged. The granular layer though often grossly thinned was represented in many of these folia. In the nodule a well-formed granular layer was present. In general, folia possessing granular cells showed a deeper molecular layer and much less glial proliferation in the cortex. In these less atrophied molecular layers the cytons of basket cells were seen to be present. The white matter in these less affected areas was, as elsewhere, heavily sclerosed but well myelinated. A superficial granular layer was a conspicuous feature of sections taken from the inferior vermis (fig. 9). The appearance of the flocculi varied from folium to folium, some having regularly arranged Purkinje cells and well-marked granular layer, others showing atrophy and heterotopia. A superficial granular layer was also present in the left flocculus.

FIG. 7.

FIG. 8.

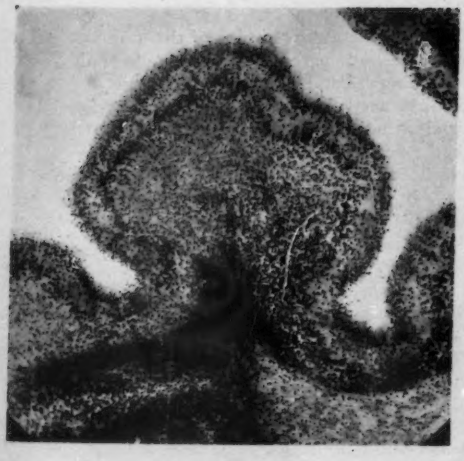

FIG. 9.

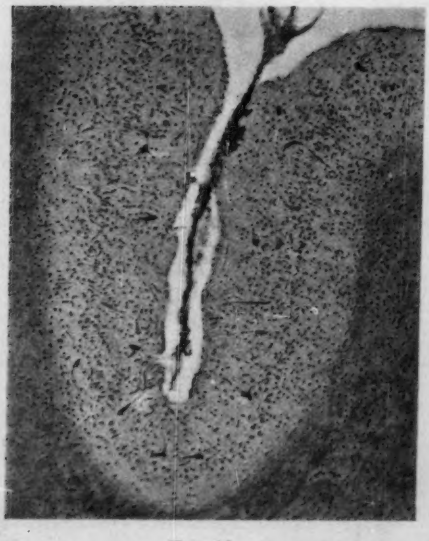

FIG. 10.

FIG. 7. (*Case* 1).—Left posterior quadrangular lobule. An atrophic folium 'Anderson's modified Kultschitsky-Pal method × 40.

FIG. 8. (*Case* 1).—Right lateral lobe. Dense gliosis in cortex of cerebellum. Holzer stain × 270.

FIG. 9. (*Case* 1).—Inferior vermis. A folium showing persistent superficial granular layer. Cresyl violet × 40.

FIG. 10. (*Case* 2).—Right anterior quadrangular lobule. Atrophy of granular layer with preservation of Purkinje cells. Cajal's silver-nitrate-alcohol-pyridine method × 60.

The *dentate nuclei* showed no outfall of cells. There was a heavy fibrillary gliosis around the nerve cells, outlining the nuclei against the less sclerosed white matter in distinctive fashion. The myelinated fibres of the grey matter appeared coarser than normal.

The *mid-brain* appeared normal. There was no atrophy or sclerosis of the substantia nigra.

In the *pons* a mild fibrillary gliosis affected the transverse fibres, middle peduncle and the grey matter of the nuclei pontis, though the nerve cells and myelinated fibres appeared normal.

In the *medulla* the nerve cells of the inferior olives were shrunken, stained poorly with aniline dyes and contained lipochrome deposits which filled about one-third of the cell body. A dense fibrillary gliosis was present around these cells and in the hila of the nuclei. No loss of myelin was observed. The pyramidal tracts showed no pathological change. There was an unusually dense subependymal gliosis. The upper segments of the *cervical spinal cord* were examined, no tract degeneration or sclerosis being found.

Cerebral cortex.—Twelve representative areas were examined from the left cerebral hemisphere. Minor abnormalities common in low-grade mental defectives were present, namely, small size and irregular arrangement of nerve cells especially in the third layer of the cortex. There was no nerve cell atrophy. A mild gliosis of fibrillary type was found in the white matter of the angular gyrus and calcarine cortex.

Thalamus, caudate nucleus, putamen and globus pallidus of the left side showed no abnormality as regards nerve cells, myelin or glia.

Case 2.—H. B., a female aged 26, was admitted to Stoke Park Colony on May 3, 1920.

Family history.—It has been impossible to trace the recent history of this family. The patient's admission papers (1920) stated that both parents were mentally and physically healthy, the father, a baker, then being 50 and the mother 60 years of age. The maternal grandparent was then alive, aged 99, the other grandparents, who were also normal, having died in their sixth or seventh decades. The patient was the second of six children and a brother, the next member of the family, appears to have suffered from the same type of cerebellar disorder. He was an imbecile who died from pulmonary tuberculosis in Brentry Colony in 1923, aged 27. Dr. Mason, the present medical superintendent, has kindly given me the following information from the available records. On admission he was described as suffering from "disseminate sclerosis" but the only evidence in support of this was a staggering gait. There was no indication of syphilis. The condition was not progressive and he was employed in domestic work requiring little intelligence. The other sibs, aged in 1920, 28, 21, 19 and 15 respectively were reported as healthy.

Past history.—Mental deficiency was first suspected in infancy. She did not begin to walk until 4 years of age and was subsequently unsteady on her feet. She started to speak at about the same time and articulation remained defective. There was no history of epilepsy.

Examination.—In 1932, at the age of 38, her mental age as estimated by the Merrill-Palmer scale of tests was 5 years 9 months. She was able to pass the majority of tests requiring finer co-ordination of movement and her copying with a pencil of a star and cross showed little evidence of lack of control. She was able to do simple knitting and bead threading. She was undersized physically. The head was small, length 166 mm., breadth 138 mm., height 118 mm., the calculated capacity being 1,116 c.mm. (about the 6-year level). Standing and sitting stature was 1,413 cm. and 78·4 cm. respectively (14-year level), and weight 48·3 kilos

(16-year level). Dynamometer readings of right and left grips were 24 and 15 kilos (15 and 12 year levels).

A neurological examination was made in 1935. Her gait was ataxic. The finger-nose test showed dysmetria in the right hand. The tendon reflexes were brisk, those of the right side of the body being exaggerated and Strümpell's sign being present in the legs. An extensor plantar reflex was obtained in the right foot. She had a slight convergent strabismus.

The patient developed phthisis in September, 1937, and died in July of the following year aged 44 years 8 months.

Post-mortem examination.—Advanced cavitating phthisis was found in the right lung, early lesions being present in the left apex. Apart from toxic changes the other visceral organs were healthy. The skull was small and thick. The meninges showed typical tuberculous meningitis with tubercles at the base of the brain and along the fissure of Sylvius. The brain was small for an adult, weighing (stripped) with cerebellum and brain-stem 928 grm. The cerebral hemispheres showed no gross lesion and their convolutional pattern was normal save for a poorly developed third temporal gyrus on the right side. The cerebellum in size and shape closely resembled that of Case 1 though there was somewhat less gaping of the sulci. The pons and medulla were also small compared with the brain as a whole, being about the same size as those of a year old infant. The weight of cerebellum with pons was 71 grm.

Microscopic examination of the nervous system.—Areas examined and staining methods employed were the same as in Case 1.

In the *cerebellum*, with certain exceptions mentioned later, the lateral lobes and vermis showed pathological changes in the main identical with those of Case 1, namely absence or gross reduction of the granular layer with relative preservation of the Purkinje cells, many of which were heterotopic in the molecular layer (fig. 10). The leptomeninges were infiltrated with endothelial cells and lymphocytes and proliferation of microglia was often seen in the molecular layer of the cerebellum. In general the Purkinje cells showed a mild degree of chromatolysis and stained poorly with cresyl violet. Impregnation methods also gave less intense results than in Case 1 and thickening and argyrophilia of the dendrites was less frequently seen. The heterotopic Purkinje cells were of the spindle or retort-shaped variety encountered in the first case and cells with triangular cytons were common. Cactus-like expansions of the dendrites were not demonstrated but the peculiar dendritic branching of plaque-like appearance was found twice in a group of Purkinje cells heterotopic in the central core of white matter in a folium of the right tonsil. Axonal torpedoes were uncommon. The thin molecular layer usually showed a narrow bundle of parallel basket fibres though the cytons of the basket cells could rarely be demonstrated. Pericellular baskets were present around the regularly placed Purkinje cells. The tangential fibres were absent in areas showing a massive atrophy of granular cells. In some of the more atrophic folia the total number of Purkinje cells were reduced but such areas were in a minority. The amount of reduction of the granular layer varied rather more than in the first case and it is probably true to say that a gross reduction rather than a total absence was the rule. The granular cells, when present, tended to be aggregated in the outermost part of the layer, subjacent to the Purkinje cells. Some of the folia of the superior part of the vermis had a recognizable granular layer and in these the molecular layer was thicker and less heterotopia of Purkinje cells was seen. As in the first case, the thicker the molecular layer the more numerous were the small nerve cells therein. The nodule was the most normal of all the areas examined. The flocculi, on the other hand, were grossly affected, some folia showing a reduction in Purkinje cells as well as absence of granular cells.

Fibrillary gliosis of the intensity met with in the first case was present in the cerebellar cortex. Folia with granular cells showed a corresponding decrease in glial proliferation. Similarly, the deeper the molecular layer the less the demonstrable gliosis. The white matter was sclerosed throughout and little or no difference could be detected between the central cores of the atrophied or less affected folia. Myelinization was poorer than in the first case, the cortical fibres staining feebly by the Kultschitsky-Pal method, while in the medullary lamellæ and central white matter a thinning of the myelinated fibres was present, though gross pallor was not seen. In sections taken from the superior vermis single myelinated fibres of coarse calibre were sometimes seen in the middle of the molecular layer. Such fibres ran parallel with the surface of the folium for a considerable distance finally ending in the central core of white matter.

In the *dentate nuclei*, while no outfall of cells had occurred, the nerve cells showed variation in size and staining properties, many colouring poorly with cresyl violet. Shrunken cells with few processes were seen in Bielschowsky preparations. The fibrillary gliosis, present elsewhere, was intensified around the nerve cells of the dentate nuclei. No pathological changes were found in the *mid-brain*. The *pons* appeared normal apart from a mild gliosis in the transverse fibres and around the nerve cells of the nuclei pontis. In the *medulla* the olives showed a slight increase in glial fibres. The nerve cells appeared normal. The pyramidal tracts were well myelinated. The restiform bodies were small, giving the medulla the appearance of being somewhat flattened in a lateral direction. The *spinal cord* was not available for examination.

No obvious pathological changes were seen in representative areas taken from the left *cerebral hemisphere*, apart from minor cell irregularities associated with imbecility. Varying degrees of toxic change were seen in the nerve cells, the most affected being the pyramidal cells of the cornu ammonis. No abnormality as regards nerve cells, glia or myelin was present in the *caudate nucleus, putamen* or *globus pallidus* of the left side.

In the left *thalamus* the nerve cells showed abnormally large lipochrome deposits and an excess of glial fibres was found in the pulvinar and beneath the ependyma.

Discussion.

Congenital cerebellar disease has often been reported in association with mental defect. Beyermann (1917) in his review of the subject suggests that it is possible to distinguish two main groups of cases, those in which the cerebellar ataxia tends to improve and those in which no improvement takes place, the latter being associated with mental retardation, usually imbecility. In the present cases the early history is not sufficiently detailed to enable one to form an opinion as to whether or not amelioration of ataxia had occurred, though when they first came under observation in the Colony signs of cerebellar disease were not very striking. It is interesting to note that in the affected sister of the first patient, who was of higher mental status, some improvement in the ataxia had taken place. It is not easy to account for the progressive course of the disease shown by the first patient during the last few years of his life, since no evidence of a recent degenerative process was discovered in the nervous system. A somewhat

similar acute terminal phase was reported by Aring (1938) in an example of the Arnold-Chiari deformity. In this case the only pathological finding was unusually numerous torpedoes in the Purkinje cell axons. Axonal swellings of this type were also present in large numbers in Case 1 (in contrast with Case 2). Although an occasional torpedo is an extremely common finding in the cerebellum in a variety of nervous diseases, their presence in such profusion is rare and it is conceivable that this widespread change may indicate a late affection of the Purkinje cells sufficiently massive to produce a further impairment of cerebellar function.

There can be little doubt that the main group of congenital cerebellar disorders is a complex one from the ætiological as from the pathological point of view. A familial incidence is not uncommon but few of such cases have been examined histologically. The present cases are, with the exception of Herringham and Andrewe's case, the only histologically verified examples of this variety of cerebellipetal atrophy which have not occurred in sporadic form. It is reasonable to ascribe a recessive mode of inheritance to such familial disorders, but up to the present there has been no adequate genetic study of congenital cerebellar atrophy. It is a curious fact that consanguinity of parents, an important criterion of rare recessive traits, has been observed only in the sporadic cases (Fickler, 1911 ; Cassirer 1912).

From the early history available in the present cases it is difficult to date the onset of distinctive cerebellar symptoms with any degree of precision. Delay in learning to walk, clumsiness and poverty of movement are not uncommon in imbeciles of no particular pathological type. The small posterior fossa of the skull shown by the first patient has been observed in congenital cerebellar ataxia by Beyermann and the histological findings in both cases leave little doubt as to the congenital or early infantile character of the affection.

The presence of dense glial sclerosis in the areas devoid of granular cells is strong evidence that the condition is one of atrophy rather than primary malformation. Embryological theories of causation involving failure in formation or migration of nerve cells with " compensatory " proliferation of the neuroglia would appear to be unnecessary and improbable in this connection since an atrophy of the granular layer of a degree comparable to that found in the present cases is known to occur in later life, for example, in juvenile amaurotic family idiocy. There are, however, microscopical signs indicative of retardation in development in the form of the persistent superficial granular layer seen here and there in Case 1 and also in the marked heterotopia of the Purkinje cells in the molecular layer

of both cases, although the latter observation is not necessarily evidence of primary malformation. Schob found displaced Purkinje cells in many different nervous diseases including senile dementia, disseminate sclerosis, paralysis agitans, general paralysis and also in areas adjoining a tuberculoma. Such heterotopic cells had often undergone considerable distortion and were present in spindle-shaped forms or with shrunken or triangular cytons. The precise mechanism of this dislocation is not fully understood. Schob demonstrated a process of basal vacuolation in the Purkinje cells and thought that this change preceded a retraction of the cell into the molecular layer. Pfeiffer (1929) in cases of general paralysis found an association between the heterotopia and inflammatory changes in the subjacent blood-vessels. It is unlikely that traction by neuroglial sclerosis by itself can be responsible for such displacement since in many conditions an intense cortical gliosis may be found in areas where the Purkinje cells are in normal alignment. If pathological factors were a common cause of Purkinje cell heterotopia one would have expected to find it more frequently in the systematic cerebellar atrophies of later life. In primary parenchymatous cerebellar atrophy, for example, this finding is exceptional. In the unusual case described by Kirschbaum and Eichholz (1932), in which the onset of ataxia began at the early age of 20, the frequent heterotopia observed among the remaining Purkinje cells was considered by the authors to be a stigma of defective cerebellar development. In the present cases the extreme degree of displacement of many of the Purkinje cells, their abnormal shape, the absence of pathological changes in the cell bodies of the sort described by Schob and the absence of discrete empty pericellular basket fibres is strongly suggestive of an arrest in migration rather than a mechanical dislocation. In folia possessing a granular layer the Purkinje cells were invariably arranged in normal fashion and it seems reasonable to assume a developmental interdependance between these two laminæ. The migration of the Purkinje cells may not be complete until shortly after birth and the disturbance created by atrophy of the granular layer occurring at this critical period might well interfere with the terminal phase of cellular organization of the cerebellum. Support is given to this view by comparing the present case with those of Vogt and Astwazaturow. In their second congenital case a diffuse atrophy of the granular layer was associated with marked Purkinje cell heterotopia in the molecular layer. In their third case in which signs of cerebellar disease appeared at a later date (head tremor at 3 years and ataxic gait at 7 years of age) the Purkinje cells were normally arranged although the granular layer was almost absent. It thus appears that time of onset of the atrophic

process in the granular layer may be decisive in bringing about irregularities in the position of Purkinje cells.

The dendritic abnormalities shown by the Purkinje cells in all probability owe their origin to a similar cause. Thickening, tortuosity and argyrophilia of the dendrites have been described in general paralysis (Arcaute, 1912), schizophrenia (Cajal, 1924; Hechst, 1930), Freidreich's ataxia (Estable, 1928), senile dementia and disseminated sclerosis (von Sántha, 1930). Cactus-like expansions with fine lateral branches similar to those seen in the present cases were also found in most of these conditions. Such formations differ from those seen in amaurotic family idiocy in that the swollen dendrites contain no lipoid deposits. Hechst and von Sántha favour the view that these changes indicate an endogenous affection of the neurone, but since a closely similar type of dendritic swelling is known to follow cerebellar traumatisms (Cajal, 1928) it appears more likely that they are reactionary in character. Bouman's (1934) conception of "hyperdifferentiation" applied by him to the tissue reactions of senile plaque formation, Alzheimer's neurofibrillary change and axonal swelling of the Purkinje cells, might well be expanded to include this variety of dendritic abnormality. In the present cases the peculiarly dense radial branching shown by some of the club-shaped expansions may perhaps be explained as an exaggerated response due to the immaturity of the Purkinje cell when exposed to the exciting pathological stimulus.

The preservation of basket fibres in the atrophied folia is a point of distinction from the type of centripetal atrophy found in amaurotic idiocy. Reference has already been made to the absence of discrete pericellular baskets in the areas showing heterotopia of the Purkinje cells, the descending branches of the parallel fibres in such situations taking the form of a uniformly spaced curtain. The parallel fibres themselves also deviated from the normal in that they were represented as a narrow bundle occupying the lower part of the molecular layer. Such an appearance is probably due to atrophic shrinkage of the tissues.

The abnormalities found elsewhere in the nervous system require little comment. The small size of brain, mediocrity of cortical structure and absence of pathological lesions are typical of many "primary" mental defectives of low mental status. It is difficult to evaluate the significance of the mild glial proliferation found in the pons in each case and the well-marked sclerosis of the inferior olives in Case 1. While it is probable that these changes are secondary to the cerebellar degeneration the possibility cannot be excluded that they are a partial expression of a genetically determined atrophy of wider systematic distribution.

SUMMARY.

Two cases of familial congenital cerebellar ataxia have been described. Both patients and their affected sibs were mental defectives. An increase in inco-ordination was observed during the last years of life in the first case; in the second the clinical condition remained stationary. Both cases came to autopsy and showed closely similar pathological findings. The brains as a whole were small. In each a small, sclerosed cerebellum of normal macroscopic configuration showed histologically a generalized and almost complete atrophy of the granular layer. The small nerve cells of the molecular layer were absent in the atrophic folia, though the parallel fibres of the basket cells were present as a narrow bundle. The tangential fibres of the granule cells were absent. Little distinction was found between the degree of affection of lateral lobes and vermis save that the nodule in both cases was the least atrophied part of the cerebellum. The Purkinje cells were relatively well preserved. Marked heterotopia of the Purkinje cells in the molecular layer was a feature of most areas and a variety of dendritic abnormality was seen including thickening, argyrophilia and cactus-like formations some of which showed peculiarly dense radial branching. Axonal torpedoes were unusually numerous in the first case. There was a dense proliferation of fibrillary neurolgia in all layers of the atrophic cerebellar cortex and generally throughout the white matter, being particularly intense round the dentate nuclei. There was some thinning of myelinated fibres, especially in Case 2, but on the whole myelin abnormalities were inconspicuous. A well-marked sclerosis of the inferior olives unaccompanied by nerve cell loss occurred in the first case. No atrophic changes were found elsewhere in the nervous system. It is concluded that the condition is an unusual type of congenital cerebellar atrophy the salient feature of which is a primary degeneration of the granular layer, the other cerebellar abnormalities found being secondary to this process. It differs from the cerebellipetal atrophy of amaurotic family idiocy not only in the absence of lipoid changes but also in the preservation af the basket fibres. It appears to be constantly associated with mental defect.

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